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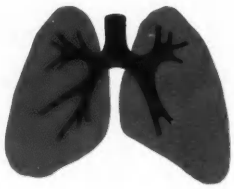

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The Prevention of the Fluid-Electrolyte "Problem" by Simple Means

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SUMMARY

Proper fluid balance may be maintained in patients after operation by the employment of simple, inexpensive procedures which may be carried out even in the smallest hospitals.

Daily weighing of patients, measurement of fluid intake and output, and knowledge of the probable electrolyte content of fluid losses are adequate guides for replacement of fluids and electrolytes. An increase in body weight is a warning of overhydration.

The content of the solution used for replacement is dictated by the route of fluid output—whether from the gastrointestinal tract, the skin, or the kidneys. Insensible losses (by perspiration and respiration) are fairly static.

Except to replace extrarenal losses, parenteral administration of normal saline solution in the immediate postoperative period is contraindicated.

Mistakes in replacement methods, especially those causing overhydration, are particularly hazardous for elderly patients.

PREOPERATIVE and postoperative management of the surgical patient has become equal in importance to surgical technique itself. The surgeon is called upon daily to apply principles of fluid and electrolyte replacement for optimum care of patients. Yet, if he reviews the current literature concerning electrolyte and fluid problems, he meets a confusing array of sodium, potassium, chloride, and carbon dioxide concentrations expressed as mill-equivalents, millimols or volumes per cent, and the everyday business of keeping a patient in balance appears a highly technical procedure. With the development of parenteral solutions of a myriad of chemical combinations, and with the accumulation of confusing experimental data involving their uses, the problem of routine maintenance seems to have become exceedingly complex. Too much emphasis is placed on how to treat patients as "fluid and electrolyte problems." It is time that emphasis be placed where it belongs, namely, on how to maintain patients properly and thus keep them from becoming problems.

The purpose of this discussion is to clarify the working principles of replacement so that they may be applied with ease and understanding. This is not to be accomplished by oversimplification, but by the application of fundamental physiological observations repeatedly verified in the clinical laboratory.

The term replacement is self-explanatory. The usual patient is in balanced state at the time of operation. Maintenance of this state throughout the postoperative course is the ideal. Until the patient is able to ingest all that is needed to maintain the balance, replacement rests in the hands of the surgeon. It can be accurately controlled by carrying out the simplest of measures. The basic requirements are a reliable set of weighing scales, an observing nurse with a measuring bottle, and an understanding by the surgeon of simple replacement principles.

The primary working guides for the surgeon are the determination of body weight, the measurement

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of fluid intake and output, and the estimation of the electrolyte losses from the skin and lungs, the gastrointestinal tract and the kidneys. The simplest of these three, *daily measurement of the body weight*, is the most important, because day-to-day changes in body weight represent gains or losses in the total water content of the body. As some 70 per cent of body weight is water, when the more or less static weight of the skeleton is considered it becomes apparent that between 70 and 80 per cent of the easily shiftable weight is water. The weight of one liter is 2.2 pounds. However, for the purposes of fluid balance a round figure of 2 pounds per liter suffices. Thus, an increase of 4 pounds in weight from one day to the next indicates that 2 liters of waters has been added to the total water content of the body.

Wangensteen,[6] in calling attention to the value of determining weight changes in controlling hydration, advocated daily postoperative weighing and placed the emphasis on anticipating and protecting against dehydration. He recognized that the effects of dehydration are not observable clinically until at least 6 per cent of the body weight is lost. However, in the author's experience the opposite situation is more to be feared — namely, the insidious accumulation of fluid, leading to deposit of water at the lung bases, perhaps with hypostatic pneumonia long before edema becomes obvious. Bladder irrigation, often necessary during the first 48 hours following urological operations, makes accurate determination of output extremely difficult. In such circumstances, oliguria or anuria may not be immediately detected when it occurs; parenterally administered fluids, especially if containing salt, are retained and a stormy postoperative course ensues. In such instances, body weight determination on the first postoperative morning would show a gain and indicate immediate evaluation of the patient's renal function. (In the presence of anuria or oliguria daily weight measurement is the great life saver, protecting against overhydration during the two weeks of recovery—the period required for repair of reversible acute renal lesions.)

A second primary function of the daily determination of weight is to permit estimation of fluid losses that cannot be measured, such as the losses in sweat or in vomitus that has missed the volumetric flask. Losses by both of these avenues are of the greatest importance not only because they result in fluid deficit but also because electrolytes in these secretions are lost as well, and body electrolyte stores hence may become rapidly depleted. Accurate estimation of such losses is quickly obtainable at the bedside by noting a fall in weight greater than that estimated from the intake-output record. This estimate of fluid loss can be exceptionally accurate when the patient's entire intake has been given parenterally in measured amounts and the urine output is known.

With early ambulation, nine out of ten patients may be placed directly on the scales at the bedside. The occasional patient who is too weak to stand or who should not be moved can be accurately weighed as demonstrated in Figure 1. The weighing litter, made to fit the platform of the scales, is constructed of plywood at a cost of a few dollars, and is light enough to be handled by an attendant. A canvas stretcher with poles removed is placed beneath the patient by the same technique that is used in changing bed sheets. The poles, shortened to fit within the bed-ends, are then placed in position and the patient lifted from bed to scales. The entire procedure requires only a few minutes and the help of two attendants or house officers.

Measurement of intake and output is next in importance. This is available to surgeons in every hospital, and accuracy is dependent entirely upon the conscientiousness of nurse and house officer. It has been the author's experience that a nurse who has been informed of the importance of this measurement becomes a cooperative aide. In making measurements of output, the route of loss—whether by urination, vomiting, gastrointestinal suction, biliary T-tube drainage, or diarrhea — should be recorded. Even if the intake and output measurements are in serious error, it is possible to carry out fairly accurate fluid and electrolyte replacement on the basis of body weight changes alone, provided the route of loss is known. The intake-output record and the determination of body weight thus act as a check-and-balance system workable in any hospital or even in the patient's home.

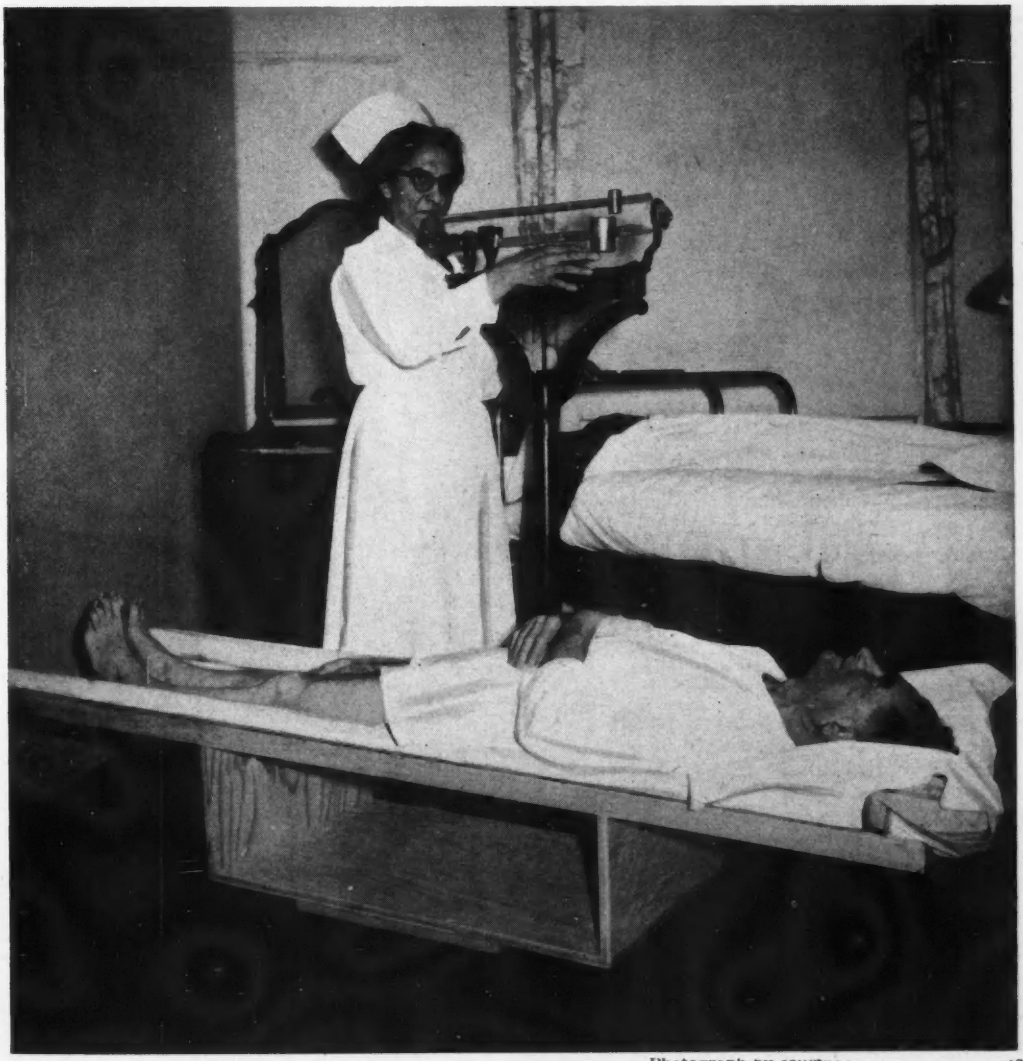
The third factor in replacement is a general knowledge on the physician's part of the channels of fluid and electrolyte loss. The accompanying chart (Figure 2) diagrammatically presents the working principles of fluid replacement in relation to route of loss. The majority of replacement solutions shown in the chart are usually in stock in a hospital supply-room. If the exact solution needed is not already made up and on hand in sterile containers (such as the solution containing 6 gm. of sodium chloride per liter) then two or more solutions which together will provide the proper amount and content of replacement fluid may be given consecutively. For example: When 3 liters of gastrointestinal content is lost, replacement may be made with 2 liters of normal saline or Ringer's solution, each liter of which contains 9 gm. of salt, and 1 liter of dextrose in water. The effective replacement, then, is 3 liters with 6 gm. of salt per liter.

To begin above and work down (Figure 2): Insensible losses are pictured as thin wavy lines, and only water is required as replacement. Daily losses by this route are remarkably constant at 500 to 800 cc., two-thirds coming from the lungs. The quantity of electrolyte present, namely salt, in the fluid thus lost is negligible from the standpoint of replacement; it amounts to less than 1 gm. per day and replacement is not necessary.

Observable sweat is pictured in the droplet form seen on the brow on humid summer days and with fever. During athletic contests, weight losses of six to eight pounds are common. Such losses are made up of 3 to 4 liters of sweat that is definitely salty.

The actual salt concentration in sweat varies greatly, ranging from 2 gm. to as much as 8 gm. per liter with an average value of somewhere between 3.5 and 4.5 gm.[3] Loss by this route may be the main cause of serious salt deficiency during prolonged shock and febrile states. (One patient who was observed recently lost eight to ten pounds during prolonged fever and shock. This weight loss represented a deficit of 4 to 5 liters of fluid with an estimated salt concentration of 4.5 gm. per liter. The clinical state of the patient did not improve until this electrolyte was replaced along with the water.) When there is visible sweat, daily losses by that route must be expected to be at least 500 cc. (in addition to insensible losses of about 800 cc.) and may be much larger. Adequate replacement with solutions at present available requires the use of half-normal saline solution, which contains 4.5 gm. of salt per liter. Here again a determination of the changes in body weight, plus a knowledge of probable salt losses in sweat, provides a basis for estimating the amount and content of solution needed for replacement.

Gastrointestinal losses of salt and water, whether by vomitus, by Wangensteen suction, by T-tube drainage, or by diarrhea, may be adequately replaced with solutions containing 6 gm. of salt per liter. With intestinal obstruction of any grade, combination of the gastric and intestinal secretions takes place so that the effective losses of the chloride and sodium ions average out as salt at 6 gm.



Photograph by courtesy of [illegible] Hospital

Figure 1.—The patient who is too sick to stand on the scales is weighed by means of a plywood cradle which fits on the platform of the usual hospital scales. He is transferred to and from the scales on a stretcher, the poles of which are removable and shortened to fit within the bed-ends.

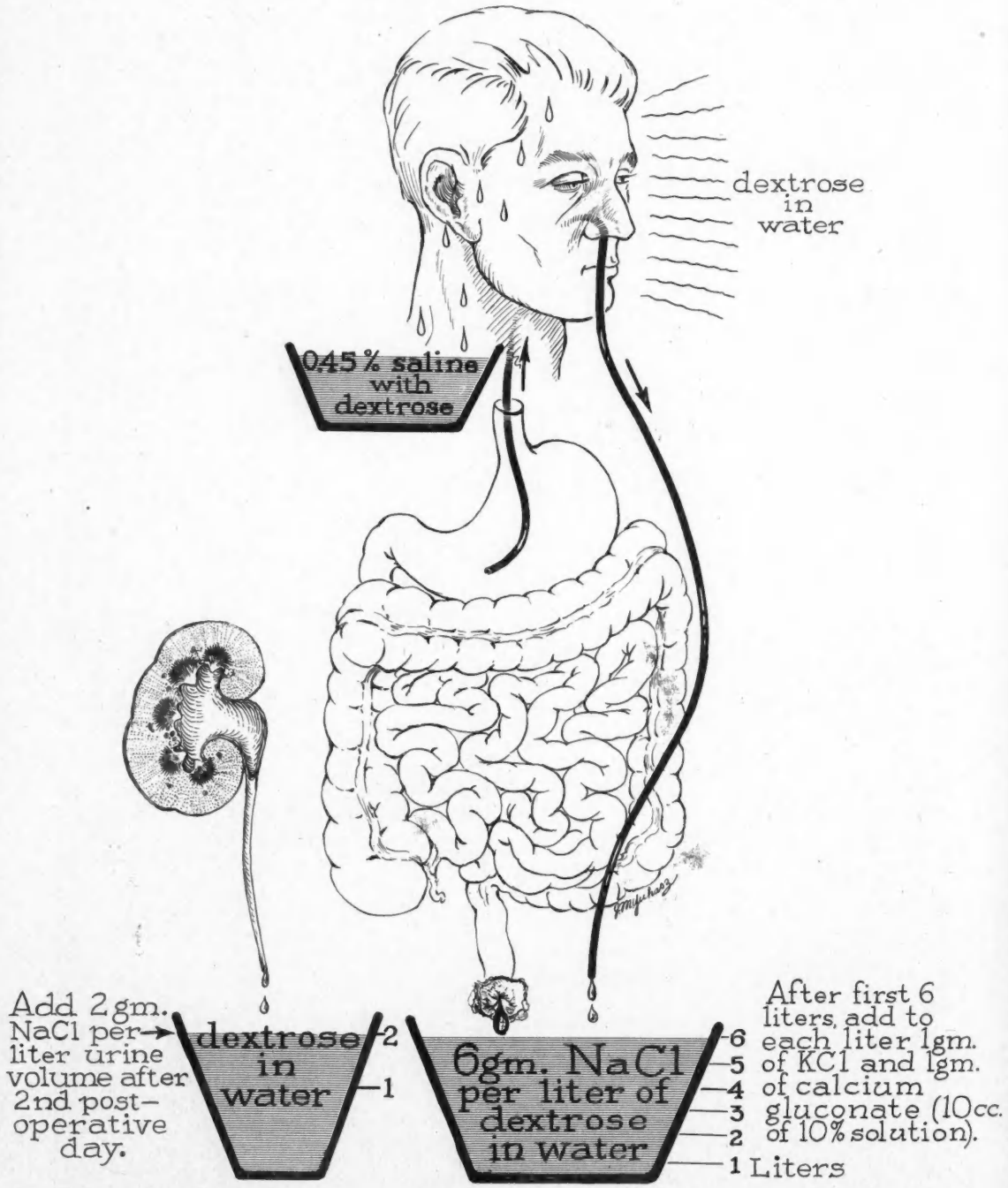


Figure 2.—Replacement requirements in terms of solutions and routes of loss.

per liter. If the usual normal saline solution (9 gm. per liter) is used for replacement, it must be administered in conjunction with dextrose in water to provide the necessary 6 gm. per liter relationship. This also holds true for Ringer's solution, which contains 9 gm. of salt per liter as well as small amounts of calcium and potassium. If losses continue for only a few days, the author uses Ringer's solution, taking advantake of the minute amounts of calcium and potassium present, which, although considerably short of actual losses of these ions, help somewhat in replacement. Quantitative replacement of gastrointestinal losses at the time of loss is mandatory.

The remaining ion of proven importance in replacement therapy is potassium. The literature has been enriched recently by much data on the use of potassium. The reports have stressed the need for adequate replacement of potassium, and at the same time have warned of dangers from its use. Unfortunately, the warning seems to have been heeded more than the need, so that the over-all result appears to be a tendency to avoid the use of potassium. Potassium is present in an average concentration of 0.5 gm. per liter in gastrointestinal secretions lost as vomitus or removed by suction. In fluid lost by diarrhea, the potassium concentration is closer to 1 gm. per liter. The great majority of patients with cellular stores of potassium of 160 gm. or more tolerate short-term losses very well. However, when these losses approach 20 per cent (20 to 30 gm.) of body stores, signs of deficit appear. This most commonly occurs with prolonged gastrointestinal suction or diarrhea during which losses have been replaced by solutions containing only ions of sodium and chloride. The vital point is that the kidney cannot conserve potassium during periods of deficiency as it is able to do with sodium and chloride. Thus, while the patient is losing 0.5 gm. of potassium in each liter removed from the bowel, he is simultaneously losing at least another 0.5 gm. in each liter of urine, despite already decreased body stores. Following trauma, shock and dehydration, urinary potassium losses tend to be 1 gm. or more per liter in spite of deficit. When large amounts of dextrose and water are given to create a large volume of urine, these potassium losses are of course accentuated. The potassium deficit may be serious and may cause a variety of mysterious symptoms long before warning of danger is given by decreased potassium concentration in the plasma. Therefore, if there is pronounced loss of gastrointestinal contents, potassium as well as sodium and chloride is required for replacement.

The intravenous use of potassium is complicated by the knowledge that high potassium levels in the plasma may cause cardiac irregularities and even cardiac arrest. The rate of injection of potassium must therefore be limited, at least until such time as extensive clinical data indicate more aggressive use of it. This is especially true if the rate of flow of the replacement fluid into the vein cannot be constantly watched. The author, therefore, follows this rule: For the first 6 liters of electrolytes and fluid removed from an adult, replace only the sodium and chloride ions. The great majority of patients do not require intubation for a longer period, and the ordinary diet quickly replaces potassium losses. But if more than 6 liters is removed and replaced with sodium chloride in dextrose, and it still appears that suction will have to be continued for an extended period, 1 gm. of potassium chloride is added to each liter of replacement solutions. (One gm. of potassium chloride supplies 0.5 gm. of potassium, so that the effective potassium replacement is 0.5 gm. per liter.) This may be mixed directly from the autoclaved dry form or added to each liter from a 10 per cent sterile solution. In order to replace calcium losses, as well as to balance the effects of the increased potassium ion during injection, 10 cc. of a 10 per cent calcium gluconate solution is also added to each liter. This procedure safely accomplishes potassium replacement of gastrointestinal losses at the time of loss.

The final and least generally understood loss which requires replacement is that from the kidney. Urine volume of 1,200 cc. daily in the early postoperative period is entirely adequate. When the patient is no longer maintained on fluid given parenterally, his oral intake may freely increase the urine output. The question of necessity for replacement of "salt losses" in the urine then arises. That the normal or moderately damaged kidney is obliged to excrete salt is a common misconception. Coller,[2] Abbott,[1] and others[4] have repeatedly demonstrated that the patient who has been operated upon tends to retain not only the body stores of salt but also any additionally administered salt and water during the first 24 to 48 postoperative hours. Each 6 gm. of salt given following operation tends to retain 1,000 cc. of water in the tissues. Because of this fluid and salt retention, with what amounts to overreplacement of the sodium and chloride ions, urine output tends to be less than in the patient receiving the same amount of fluid as dextrose in water. Perara[5] has further shown that the elderly hypertensive patient tends to retain sodium chloride and is able to remain on a relatively salt-free diet for months to years. This implies that with vascular changes of aging but with normal kidney function as measured by phenolsulfonephthalein excretion and by nitrogen content of the plasma, the tendency to retain the sodium ion is increased. Since the elderly patient may be adversely affected if overhydration occurs, especially during the early postoperative period, the routine use of normal saline parenterally at this time, unless specifically needed for replacement of extrarenal salt losses, is to be condemned. (The author observed one elderly man in whom gross edema developed insidiously during a 12-day period because of routine use of 1 liter of normal saline solution daily. A postoperative weight chart—he had gained 14 pounds—would have called attention to the fluid retention in time.) When parenteral replacement is necessary beyond the second postoperative day, the author provides sodium chlo-

ride in amount sufficient to permit excretion of 2 gm. per liter of urine. Thus, with the urinary output ranging around 2 liters, the daily intake of salt parenterally is restricted to 4.5 gm., usually given as a liter of half-normal saline solution in dextrose or as 500 cc. of normal saline solution.

Replacement of blood lost during or after operation requires only brief discussion. Optimum care demands replacement of whole blood at the time whole blood is lost. When the weighing of sponges or other means of measurement of blood loss cannot be carried out, the judgment of the surgeon must suffice. Care must be taken not to give too much blood. Abnormally high blood volume is as much to be feared as is retention of fluid; it may lead to cardiac failure. Red cell mass alone may be used to replace blood lost postoperatively, save in the case of acute hemorrhage. An elderly patient, even one in only fair nutritional state, will recoup plasma losses from body stores and from diet within the 24 hours after operation if hydration is maintained.

Special attention should be called to the differences between elderly patients and younger ones with regard to replacement of fluids parenterally. Primarily, the older patient has less capacity to tolerate mistakes in replacement, especially those connected with the routine and overenthusiastic administration of salt and water. With salt retention in the early postoperative period, fluid is more liable to collect at the site of operation and in the easily distensible tissues. A little fluid at the lung bases may lead to hypostatic pneumonia; visceral edema may lead to nausea and dietary problems; increase in plasma volume may cause cardiac decompensation. In addition, trauma and shock are considerably more liable to result in kidney damage in elderly than in young patients. Oliguria associated with rising nitrogen levels in the blood following operation is far more common in elderly patients than is generally recognized. Anuria of the lower nephron type must always be anticipated following a period of shock, especially in the older patient. With routine parenteral administration of 3,000 cc. of fluid per day, signs of fluid retention are certain to develop. Measurement of body weight and conservative hydration will protect the patient in such circumstances.

DISCUSSION

On the basis of the data presented, the postoperative fluid demands of the average patient are met with 2,000 cc., which allows 800 cc. for insensible perspiration and 1,200 cc. for urine production. The great majority of patients are taking food by mouth on the third day, and parenteral fluid administration then is no longer necessary. Losses in formed feces are disregarded, as they are counterbalanced in the main by water produced from the combustion of fat, carbohydrate, and protein. The only indication for the use of salt solutions during the first 48 postoperative hours is for replacement of extrarenal losses, and that replacement must be prompt and quantitative. Plasma electrolyte determination by laboratory tests is rarely necessary unless day-to-day replacement has been neglected.

CONCLUSIONS

Adequate replacement of fluid and electrolytes requires the use of simple and easily available measures. They are measurement of body weight, measurement of intake-output, and knowledge of probable electrolyte content of fluid losses.

Adequate replacement solutions are:

—for insensible losses—dextrose in water.

—for gastrointestinal losses — 6 gm. of sodium chloride per liter of water to replace the first 6 liters of fluid lost. Following this, 1 gm. of potassium chloride plus 1 gm. of calcium gluconate (10 cc. of 10 per cent solution) is added to each liter.

—for observable perspiration—half-normal saline solution.

—for urine excretion—dextrose in water for 48 postoperative hours. With urine volume of 2 liters and adequate kidney function, 1 liter of half-normal saline daily thereafter, in addition to dextrose in water.

Use of normal saline solution parenterally in the early postoperative period is contraindicated in the absence of extrarenal salt losses.

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Considerations of Postoperative Electrolyte and Fluid Replacement

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SUMMARY

The most important postoperative fluid considerations are maintenance of adequate urinary output, of blood volume, and of extracellular and interstitial cell water and electrolytes.

Normal urinary output is between 1,000 and 1,500 cc. daily. A fluid intake of 2,000 cc. of 5 per cent dextrose in distilled water, plus 500 cc. of normal saline solution, will insure this amount of urinary output.

The use of 5 per cent dextrose solutions in distilled water provides fluid, retards the protein catabolism of the body, and spares electrolytes.

Irradiated plasma is the only intravenous solution which will adequately supply protein in amounts to maintain nitrogen equilibrium. Protein hydrolysates in the absence of adequate caloric intake do not provide enough protein for nitrogen balance.

The role of the potassium ion is ordinarily not a consideration in postoperative fluid management. It becomes a consideration in the presence of a large amount of drainage from wounds or abscess cavities, nasogastric suction, or intestinal fistulae. It also must be given attention in cases in which parenteral administration of fluids is necessary for a prolonged period.

FORTUNATELY, ideas of postoperative fluid management have undergone considerable change in the past few years. The experimental approach to such problems and experience in dealing with them have changed, for the better, the indications for the use of various fluids postoperatively. Patients should be prepared for operation with normal hydration, blood volume, hemoglobin concentration, electrolyte and nitrogen equilibrium and with normal renal function. Postoperative fluid therapy is greatly complicated if preoperative deficits must be dealt with simultaneously with postoperative fluid requirements.

In general, surgical procedures interrupt the normal body functions by affecting blood volume, hemoglobin concentration, plasma proteins and electrolyte concentrations. And, in general, postoperative care is directed toward replacing the abnormal fluid losses which may be incurred during the operation or which may follow in the postoperative period from vomiting or mechanical withdrawals from the gastrointestinal tract, from abnormal losses through fistulae in the intestinal or urinary tract, from excessive tissue and fluid drainages, or from subsequent alterations in fluid adjustments attendant upon these changes.

Fluid and electrolyte replacement is based upon considerations of several anatomical and physiological factors. First, the extracellular fluid compartment. This compartment is recognized as that space or potential space in which electrolyte ions and protein molecules interchange between vascular capillaries and tissue cells. The fluid in the compartment is made up of plasma and interstitial fluid. The interstitial fluid may move into the general circulation to maintain plasma volume following shock from blood loss, or it may increase greatly due to upsets of electrolyte equilibrium or of osmotic pressure and be manifested as edema. Second, normal renal function must exist for the proper removal of the products of metabolism and for the delicate adjustment of acid-base balance. Third, losses of protein, water, and electrolytes must be measured accurately if replacement is to be accurate. Fourth, caloric requirements of the individual must be understood in order that the need for replacements may be computed.

The goal in postoperative fluid therapy is to maintain normal renal function and to prevent upsets of electrolyte balance which may produce alkalosis or acidosis. Of secondary importance is to restore by parenteral means caloric requirements or the protein losses attendant upon the surgical procedure or upon the disease which necessitated operation. The patient whose gastrointestinal tract can receive fluids and who loses electrolyte only through renal filtration and who has no protein loss from wound drainage or fistulae of various kinds, is not a difficult problem. But loss of these substances, through hemorrhage, vomiting, diarrhea, fistulae, or purulent drainage, increases the difficulty of replacement.

Maintenance of renal function is one of the first postoperative considerations. Closely associated with satisfactory renal function is the ability of the kidney to excrete or conserve sodium. It is a frequently observed fact that during the 24 hours following following major surgical procedures, there is a temporary decrease in urinary output, no matter how much parenteral fluid is added to the circulation. During this same period less sodium chlo-

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ride is excreted by the kidneys. Fluids in excess of blood volume requirements will therefore be held in the interstitial fluid compartment, and the salt not excreted by the kidney will also find its way into this compartment. This in turn will attract more fluid in the extracellular space in response to osmotic changes incident to increased ionic concentrations. Therefore, in the immediate postoperative period, fluid should not be in excess of that needed to replace body water stores, and such fluids as are given should be low in salt content.

Adequate urinary output is approximately 1,000 to 1,500 cc. daily. An intake of 2,500 cc. of fluid in 24 hours will provide for a urinary output of this amount, if the patient has no abnormal fluid loss. The normal daily salt requirement is between 4 and 5 gm. (18 to 36 gm. of sodium chloride was administered almost routinely 12 to 15 years ago). Rather careful studies of the concentrations of sodium chloride in the urine recently have been made in normal individuals maintained on fluids given parenterally.[2,3] These studies showed that sodium chloride administered in excess of 4 to 5 gm. daily will appear in the urine. When renal function is impaired, excesses of sodium and chloride will be held in the interstitial fluid with the previously mentioned effects. Five per cent dextrose in distilled water is an isotonic solution; 2,000 cc. of this solution plus 500 cc. of normal saline solution daily will provide necessary hydration and satisfy normal salt needs.

Abnormal fluid loss through gastric suction, biliary drainage, or fistulae, must accurately be measured and the amount added to the figure of 2,500 cc. in order to hydrate the patient adequately. The amount of electrolytes lost through these abnormal means should be calculated and replaced by intravenous injection of a solution containing them, or by adding needed ions to a solution for intravenous use.

The principal intracellular electrolyte is potassium. This electrolyte commonly is excreted in the urine in small amounts at a steady rate, and the excretion rate continues if no potassium is supplied to the body. Such losses can be sustained by the body for seven to 10 days without any replacement. Potassium excretion is tied up with the protein metabolism. Excessive potassium loss should be borne in mind in dealing with large protein losses such as occur in patients who have extensive abscesses or severe burns. Potassium losses also are greater than normal in patients who have bowel obstructions which persist for more than a few days, when nasogastric suction is employed for extended periods, or when intestinal fistulae discharge a large amount of fluid. In cases of that type, it should be recognized that potassium deficiency may exist before serum levels decrease. If the abnormal fluid losses previously mentioned can be measured accurately, the potassium loss can be calculated. But if the loss is contained chiefly in dressings, analysis of these for potassium is more difficult and calculation then depends upon known average losses in the various fluids. In replacement of potassium it should be borne in mind that the kidney excretes potassium at a steady rate. If too much potassium is supplied at one time by intravenous means, potassium intoxication may occur from elevation of the serum potassium. In conditions of anuria or oliguria, potassium replacement should be undertaken cautiously to avoid potassium excess.

One of the most important factors in postoperative fluid management is the replacement of blood lost at operation or the replacement of blood lost in concealed hemorrhage after the operative procedure has been completed. Blood losses of less than 500 cc. usually can be tolerated without prolonging convalescence, and replacement will not be necessary. A practical way to measure blood loss is by hematocrit measurement of packed red cells before operation and comparing it with the measurement on the third postoperative day. If the hematocrit shows a fall of more than 5 points on the third postoperative day, more than 500 cc. of blood has been lost and transfusion is needed. Stanton and coworkers[5] measured blood loss at operation as carefully as could be done and correlated the hematocrit measurement with blood volumes, red cell counts and hemoglobin determinations. They concluded that the hematocrit reading was the most practical and the simplest method of determining blood loss. Certain cholecystectomies and hysterectomies are often associated with greater blood loss than is apparent during the procedure, and in many of these operations transfusions should be given following operation to correct for these losses. Both blood volume and hemoglobin concentration should, of course, be brought to normal levels before major operation is undertaken.

CALORIC AND PROTEIN REQUIREMENTS

The problem of maintaining caloric and protein requirements has received much attention in recent years. The clue to proper management lies almost entirely in the field of preoperative preparation of the patient. A patient in a state of good nutrition can tolerate without difficulty a few days of relative starvation. It is known that a few grams of dextrose administered to a starving patient will greatly decrease his rate of catabolism and nitrogen excretion. Two liters of 5 per cent dextrose in distilled water will provide 100 gm. of dextrose or 400 calories. This amount of dextrose will greatly spare the protein loss. Two hundred gm. of dextrose provided in 2 liters of 10 per cent dextrose in water will not appreciably further decrease the protein breakdown and a good portion of the extra dextrose administered will be excreted in the urine.[2] Great efforts have been made to provide enough protein parenterally in amounts greater than are excreted as urinary nitrogen. This can best be done by the administration of irradiated plasma in 1,000 to 2,000 cc. amounts.[1] The cost of such administration is almost prohibitive and the effectiveness of therapy requires determinations of total circulating protein and careful quantitative analyses of all body excretions and drainages. Laboratory facilities to do this are not

ordinarily available. It should be emphasized that serum or plasma protein concentration values have little clinical significance if the plasma volume is unknown. A person in a starvation state may have normal plasma protein concentration because of decrease in plasma volume.

Protein hydrolysates are metabolized chiefly as calories even when administered with dextrose solutions, and have little effect in decreasing the nitrogen excretion. Used as supplementary nitrogen to an adequate oral caloric intake, they will be metabolized as protein.

At present there is no satisfactory method of providing calories parenterally in amounts large enough for minimal daily requirements. If 10 per cent dextrose solutions were used, 4,000 to 5,000 cc. daily would be required. If this amount of fluid were given in a 24-hour period, a large portion of it would be lost in the urine. A great many more calories may be provided in the simplest type of oral feeding as soon as the alimentary canal can function postoperatively. The alimentary canal also provides the quickest and best avenue of assimilating protein.

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NOTICE

Notice of the source of the photographs used with the article Cancer of the Skin by Harry J. Templeton, M.D., which was a part of a trilogy on Malignancies of the Skin in the September issue of CALIFORNIA MEDICINE, was inadvertently omitted. The pictures were supplied by the Alameda County Highland Hospital Cancer Clinic.

Results of Irradiation in Cancer of the Lip, Tongue and Ear

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SUMMARY

Cancer of the lip: The primary lesion can be controlled by irradiation in approximately 80 per cent of cases. For lesions with metastases there is only about a 25 per cent chance of five-year arrest (irradiation of the primary lesion followed by excision of involved nodes).

Cancer of the tongue: Lesions in the anterior two-thirds are controllable by irradiation in about 50 per cent of cases if the nodes are not involved; the salvage is only about 15 per cent if the nodes are involved (nodes treated surgically). Lesions in the posterior third of the tongue are seldom controlled in the authors' experience.

Cancer of the ear (auricle): Five-year arrest of basal-cell lesions should be attained by irradiation in about 80 per cent of cases; of squamous-cell lesions in about 60 per cent. If the lesion is extensive, radiation does not offer a superior cosmetic result to operation and entails danger of late chondronecrosis. Therefore extensive lesions are probably best treated surgically. In either event, it appears probable that results of irradiation can be improved by the use of more adequate fields and greater fractionation.

THERE have been almost as many ways of treating epidermoid cancer of accessible sites as there have been men doing it. The authors believe, on the basis of some 20 years of clinical experience, that the cosmetic and functional results of correctly used radiation are in general superior to those obtainable by other known methods. At the same time, it is readily agreed—and emphasized—that the cure of some minute and questionable lesions is often best achieved by the simple excisional procedure necessary for biopsy, and that very advanced lesions with bone involvement may best be handled by truly radical operation. Between these two extremes lie most cases—those in which irradiation is believed to be the method of choice.

If there is clinical evidence of limited lymph node involvement, surgical removal of the nodes is usually indicated. If involvement is extensive or the nodes appear clinically to be inoperable (deep, fixed, etc.), irradiation will provide temporary control in a fair number of cases and permanent arrest in a few. Prophylactic neck node dissection has not been recommended on the Stanford Service at the San Francisco Hospital.

Lesions recurrent centrally after previous irradiation are usually best treated by excision or electrocoagulation; those with marginal recurrence, or recurrence after inadequate dosage, may sometimes be cured by radical re-irradiation.

The following report is a summary of the early and late results of irradiation in the treatment of cancer of the lip, tongue and ear at the San Francisco Hospital and in the authors' private practice during the 17 years 1932-1948 inclusive. Most of the lip lesions, all of the tongue tumors and many of the ear lesions were verified by microscopic examination. Almost all of the biopsied lip lesions were squamous-cell carcinomas; the tongue lesions were squamous-cell tumors; the ear lesions were basal, basosquamous or squamous-cell carcinomas.

Many of the patients, especially those observed at the San Francisco Hospital, had advanced lesions with metastases at the time of admission. Usually in such cases only palliative irradiation was given. Other patients had recurrence of lesions previously treated elsewhere. A few had multiple lesions (face, eyelids, ear, etc.). The most noteworthy in this group was a man, 74 years of age, with 14 different basal-cell cancers on the head.

Attempts were made to follow the results in as many patients as possible. This was readily accomplished in those cases early in the series in which the treatment failed, notably in cases of tumor of the tongue. A goodly number of the patients were elderly persons who died of intercurrent disease before a five-year follow-up period had elapsed.

In cases of involved, inoperable nodes external roentgen therapy to skin tolerance was given. If the lesion was operable, the patient was referred for surgical treatment.

The care and the after-care of skin and mucosal reactions were conducted along conservative and expectant lines.

CANCER OF THE LIP

Material. One hundred and twenty-one patients were observed; 105 had a full course of treatment. Eleven of the patients when first observed had recurrence of lesions after previous treatment elsewhere, two by roentgen therapy, two by radium therapy and seven by operation. (The two who had had radium therapy and the seven who had had operation had been given that treatment elsewhere in private practice.) Of the fully treated patients, eight had lymph node involvement on admission, and node involvement developed in two others subsequent to treatment by the authors.

Read by invitation before the San Francisco Surgical Society in November 1949.

Clinical Stages. In 108 cases the records showed staging as follows:

	Size of Tumor	S. F. Hospital	Office	Total
Stage I	Less than 3 cm.	21	48	69
Stage II	3 to 5 cm.	8	16	24
Stage III	Over 5 cm.	4	1	5
Stage IV	With metastases	9	1	10

Treatment Dosage. Patients with lesions of the lip were treated by fractionated roentgen therapy, using 100 to 200 KV, HVL from 1 Al to 1 Cu, depending on the thickness of the lesion, 200 to 500 r daily for a total dose of from 4,000 to 6,000 r air in one to four weeks.

Reasons for Incomplete Treatment. These included: Advanced tumor in feeble or moribund patient; advanced tumor in patient with distant metastasis; tumor persistent after previous incomplete irradiation elsewhere; irresponsible patient who did not keep appointments; anxiousness of referring surgeon to resect a slowly receding tumor; and development of complications (pneumonia, etc.) during treatment.

Results of Treatment (Table 1). Treatment was completed in 105 cases. In three patients (all with advanced lesions) the lesion was not arrested; two died in one month, one in five months. The other 102 showed initial arrest. In seven cases there was recurrence. Of these, three were marginal recurrences which were re-irradiated and arrested; two were resected and arrested; two were not controlled and the patients died.

In the treated group were 100 patients who, as far as could be traced, remained well for from two to 18 years. Six of them subsequently died of intercurrent disease* (with the lip well). Of the 62 patients observed prior to 1944, 25 have been followed. Five of them are known to have died with cancer and 20 are known to be well. The known five-year arrest rate is therefore 80 per cent. Some of the 37 patients not personally seen have been traced by letter and are reported to be well. None of those so traced were reported to have died with the disease or to have had recurrence, and it is believed reasonable to assume that the arrest rate for the entire group was at least as high as the arrest rate for the completely followed group of 25 (80 per cent).

Reasons for Recurrence. These are believed to be, principally, inadequate size of field irradiated, inadequate dosage, and advanced stage of disease before treatment.

Complications. In one case necrosis of the lip was reported to have developed eight years after treatment. The patient was a male, 60 years of age, with a Stage IV recurrent postoperative lesion. It was given 4,000 r in 33 days in 1940. In 1948, while the patient was under custodial care at Napa State Hospital, "breaking down" in the center of the formerly treated area was reported by telephone. Further details are lacking. The mental status of the patient was such that factitial ulcer was not unlikely.

Results Reported in the Literature. The most informative recent reports are those of Ebenius and of Paterson (Table 2). Both reported five-year arrests of 65 per cent by radiation, in a total of some 953 cases. Of 541 primary cases, Ebenius arrested 80 per cent, and in 208 cases with metastatic nodes apparent arrest both in primary lesion and nodes was obtained in 25 per cent. The best comparable surgical data indicate similar results (65 per cent relative five-year arrests, all treated cases—Sistrunk and co-workers).

Ebenius limited his report strictly to cases of cancer of the vermilion surface of the lip, excluding cancer of the skin at the vermilion border and cancer of the buccal mucosa invading the lip. His data show the increasing use of irradiation in the control of the lip cancer in Sweden over two decades and the excellent cosmetic results obtainable. As in the cases reported upon herein by the authors, the lower lip was involved in 99 per cent of the cases in Ebenius' series.

Metastases were treated by roentgen irradiation and, after three weeks' rest, surgical excision. Recurrences were treated mostly by excision. Radiation necrosis of the lip developed in 8 per cent of cases. In two-thirds of these the necrotic area healed with conservative local treatment; in one-third, excision was carried out.

Concerning the results of neck dissection, Cross and co-workers reported that 36 per cent of patients with neck dissection and pathologically verified

*One each at two years (carcinoma of the prostate), three years (bronchogenic carcinoma), five years (cause unknown), seven years (miliary tuberculosis), 11 years (bronchopneumonia), 12 years (arteriosclerosis).

TABLE 1.—*Cancer of the Lip (1932-48)*

	No. of Cases	Treatment Completed	With Nodes on Admission	Arrested at End of Treatment	Recurrence	Nodes Developed After Treatment	Radiation Necrosis
Hospital	55	39	8	36	4 (6 mo. 1 yr. 2 yr. 3 yr.)	1 (10 mo.)	1 (?) 8 yr., lip
Office	66	66	0	66	3 (10 mo. 20 mo. 2 yr.)	1 (9 mo.)	....
Total	121	105	8	102	7	2	1 (?)

TABLE 2.—*Cancer of the Lip (Reported in the Literature)*

Author	No. of Cases	Treatment Completed	With Nodes on Admission (Per Cent)	Relative 5-yr. Arrests (Per Cent)	Recurrence (Per Cent)	Nodes Developed After Treatment* (Per Cent)	Radiation Necrosis (Per Cent)
Ebenius	807	778	15	64.9†	7	9	8
Paterson (1946)	175	175	....	65.0	..	..	..

*Duffy, Widmann, Engelstad, Bergendal, Martin and others give average 30 per cent incidence of metastatic nodes (all cases); however, in primary cases treated, node involvement developed in only about 8 per cent.

†Note: The relative five-year arrest rate for 541 primary cases was 80.5 per cent; for 208 cases with metastases, 25.5 per cent. Data regarding the remaining 89 cases of the 778 are not available.

node metastases from lip cancer survived three years.

CANCER OF THE TONGUE

Material. Seventy-one patients were observed; 57 completed treatment as planned. Eleven of the patients had recurrence after treatment elsewhere (eight following irradiation, and three following operation). Twenty-nine had lymph node involvement on admission and in nine others node involvement developed subsequent to treatment by the authors.

Clinical Stage. In 61 cases the records showed staging as follows:

	Size of Tumor	S. F. Hospital	Office	Total
Stage I	Under 3 cm.	6	5	11
Stage II	3 to 5 cm.	4	3	7
Stage III	Over 5 cm.	14	1	15
Stage IV	With metastases	25	3	28

Anatomical location was as follows:

	S. F. Hospital	Office	Total
Anterior 2/3 of tongue	19	10	29
Posterior 1/3 of tongue	20	7	27
Both locations or unclassified	10	5	15

Treatment Dosage. For cancer of the tongue, external roentgen therapy was given to skin tolerance (approximately 3,000 r to each side), followed by intraoral roentgen or radium therapy, to an estimated tumor dose of 5,000 to 6,000 r in four weeks.

Results of Treatment (Table 3). Of the 57 patients who completed treatment, many were frankly incurable from the start, but were given treatment which in the authors' experience has occasionally resulted in long arrest even of advanced lesions. In only 28 was primary arrest obtained; in ten of these there was subsequent recurrence, and in one radiation osteitis developed. The patient with radiation osteitis was a 64-year-old male who had a Stage III cancer of the left side of the middle third of the tongue. In May 1947 he was given external and intraoral roentgen irradiation (2,200 r and 4,400 r respectively) with apparent control. In March 1948 enlarged nodes developed in the left upper cervical region. The patient refused excision of them and 3,850 r was delivered in three weeks to a left lateral cervical field. In February 1949 left oral pain developed. Roentgenograms showed mandibular sclerosis and porosis (presumed to be radiation osteitis). The patient died in June 1949 with node and lung metastases.

In 35 cases treated prior to 1944 there were six known five-year arrests (17 per cent). Three patients died of intercurrent disease, without evidence of local recurrence.

Palliation. The arrest rate is low in tongue lesions. Palliation is often achievable, however, with adequate dosage. Some of the patients treated by the authors received less than 3,000 r tumor dose and were not greatly helped. With regard to the patients treated at the hospital the following observation was made:

Stage III cases: Nine had over 3,000 r tumor dose; four were controlled (two temporarily, two more than five years). Five had less than 3,000 r and none were controlled.

Stage IV cases: Thirteen had over 3,000 r tumor dose; temporary control of the primary lesion was observed in five cases. Twelve had less than 3,000 r, none with control.

Results in the Literature (Table 4). Jacobson reported results with irradiation in 277 cases. Of 103 primary cases, 52 were arrested; of 130 cases with metastasis, 15 were arrested. The relative five-year arrest rate for all cases was 28 per cent. The dosage (in roentgen treated cases) was approximately 5,500 r tumor in 17 days. Paterson reported an identical five-year arrest rate in 465 cases (28 per cent).

TABLE 3.—*Cancer of the Tongue (1932-48)*

	No. of Cases	Treatment Completed	With Nodes on Admission	Arrested at End of Treatment	Recurrence	Nodes Developed After Treatment	Radiation Necrosis
Hospital	49	37	23	18 (including 4 with nodes)	10	7	1 (bone)
Office	22	20	6	10 (including 2 with nodes)	?	2	..
Total	71	57	29	28	10	9	1

TABLE 4.—*Cancer of the Tongue (Reported in the Literature)*

Author	No. of Cases	Treatment Completed	With Nodes on Admission (Per Cent)	Relative 5-Yr. Arrests (Per Cent)	Recurrence (Per Cent)	Nodes Developed After Treatment (Per Cent)	Radiation Necrosis (Cases)
Jacobson (1948)	318	277	48	28*	11	12	4 tongue 10 skin 15 jaw
Paterson (1947)	.....	465	....	28	....	....	....
Peterson (1948)	.....	105	58	23	....	9	....

*Note: The relative five-year arrest rate for 103 primary cases was 52 per cent; for 130 cases with metastases, 15 per cent. Data regarding the remaining 44 cases of the 277 are not available.

The Radium Institute (Paris) is reported by Ackerman and Regato to have had the following results:

Location of Lesion		
Anterior 2/3 (494 cases)	56 per cent without recurrence during subsequent course	23 per cent well and free of disease after five years
Posterior 1/3 (127 cases)	.....	5.5 per cent well after five years

CANCER OF THE EAR

Material. Twenty-five patients were observed; 23 completed treatment. Five of the patients had recurrence following treatment elsewhere (one after irradiation, four after operation).

Basal-cell lesions predominated. The biopsy diagnosis in 12 cases was basal-cell; in three, basosquamous; in two, squamous. In the rest of the cases the diagnosis was just listed as "cancer" and no biopsy report could be traced. However, it is only fair to add that all patients were referred, and had been observed usually by experienced surgeons, dermatologists or other clinicians prior to treatment. Further, as Ebenius pointed out, while biopsy is always desirable for the record, it is not always essential and may even be misleading. Most cancer workers have seen pathological reports of definite cancer subsequently revised to "nonmalignant process" at the five-year follow-up review; conversely, patients on whom the biopsy report was "no evidence of cancer" may subsequently have extension or metastasis—the original biopsy specimen having been inadequate or from a benign portion of the lesion. These remarks are in elucidation and not defense. Published data should be biopsy-proven whenever possible.

Clinical Stage: In 23 cases the records showed:

	Size of Lesion	S. F. Hospital	Office	Total
Stage I	Under 1 cm.	3	6	9
Stage II	1 to 3 cm.	2	6	8
Stage III	Over 3 cm.	2	3	5
Stage IV	With metastasis or bone involvement	0	1	1

Three cases of cancer of the skin deep in the external auditory canal are not included, since this report deals only with cancer of the external ear or auricle. The auditory canal lesions tend to be diagnosed late, to entail bone involvement, and to be highly incurable by any means.

Treatment Dosage. Lesions of the ear were treated by roentgen therapy in a manner similar to that used for lip lesions.

Results of Treatment (Table 5). Primary arrest was obtained in all of the 23 cases in which treatment was completed. Recurrence is known to have taken place in three patients. One was re-irradiated and resection was done later, one was referred for operation but not traced further, and one could not be followed. In this last case, recurrence was reported by telephone eight years after treatment. The patient refused examination and care by the authors.

Ten patients are known to have had arrest of from one to five years. Of 12 patients treated prior to 1944, it has been possible to trace only two; one with known five-year arrest and one with recurrence. The rest of the 12, followed for shorter periods, are presumed but not known to be well.

Results in the Literature (Table 6). Cancer of the ear is not common and it is difficult to find any large reported series of cases. Strandquist reported 16 of 22 cases arrested for one to six years (73 per cent). In the remaining six cases there was persistence or recurrence, and in five of the group variable degrees of radiation necrosis developed. In three of seven cases of squamous-cell tumor, the growth metastasized to nodes.

Spencer reported treatment of eight advanced recurrent cases with poor results. After reviewing his own work and the recent literature he concluded that while early cancer of the auricle involving the helix is quite curable, advanced cancer (especially cancer arising in the external auditory canal) is not.

Tice and White reported some 29 ear lesions in a group of 358 patients with biopsy-proven skin

TABLE 5.—*Cancer of the Ear (1932-48)*

	No. of Cases	Treatment Completed	With Nodes on Admission	Arrested at End of Treatment	Recurrence	Nodes Developed After Treatment	Radiation Necrosis
Hospital	7	6	0	6	1 (16 mo.)	0	0
Office	18	17	0	17	2 (10 mo. 8 yr.)	0	1
Total	25	23	0	23	3	0	1

TABLE 6.—*Cancer of the Ear (Reported in the Literature)*

Author	No. of Cases	Treatment Completed	With Nodes on Admission	Arrests (1-6 yr.)	Recurrence or Persistence	Nodes Developed After Treatment	Radiation Necrosis
Strandquist (1944) ..	.....	22	1	16	6	2	5 (4 spontaneous healing, 1 excision)
Tice (1948)	.....	29	....	88% basal-cell 59% squamous-cell	....	....	.....

cancers. Of the basal-cell lesions "88 per cent" were arrested, and of the squamous-cell "59 per cent." "Twelve per cent" of the basal-cell and "41 per cent" of the squamous-cell lesions recurred. These therapists used short intensive roentgen therapy (1,250 r x 4, 90 KV, HVL approximately 1 Al, total dose 5,000 r in one week). The over-all arrest rate was 95 per cent for the basal-cell and 80 per cent for the squamous-cell skin lesions. Radiation ulcers occurred in 4.6 per cent of the entire group.

Dr. N. J. Howard of San Francisco in an unpublished report of a series of squamous-cell cancers of the auricle noted a high incidence of recurrence or cervical node involvement. He favored radical operation and neck dissection.

CASE REPORTS

CASE 1: A man 73 years of age had squamous-cell carcinoma of the lower lip, measuring 3 x 2.5 x 4 cm. There was clinical and microscopic evidence of muscle invasion. There was an enlarged, firm left submental node about 1.5 cm. in diameter. The plan of treatment decided upon was to irradiate the primary lesion and to follow with neck dissection. Twenty doses of 200 r each to a field 4 x 6 cm. in diameter over the lower lip, using 200 KV, HVL 1 mm. Cu, at a distance of 50 cm., were given in October 1941. Resection of the node was advised but refused and the node was given 20 doses of 200 r to a field 6 cm. in diameter. The tumor dose was approximately 4,500 r in three weeks. The growth has been arrested nine years to date.

CASE 2: A 69-year-old man had squamous-cell carcinoma of the lower lip, proven by biopsy. Eighteen doses of 300 r each were given to an area 6 x 3 cm. in diameter (ending with 6 x 2 cm.), using factors similar to those in Case 1, in October 1938. The tumor dose was approximately 6,000 r in three weeks. The growth has been arrested 11 years to date.

CASE 3: A man 58 years of age had squamous-cell carcinoma of the right side of the tongue, middle third. Radiation was given, 4,500 r right extraoral and 4,200 r left extraoral, in January, February and March 1935, to fields 9 to 7 cm. in diameter, using 200 KV, HVL 2 mm. Cu. In May 1936, a small remaining nodule was excised. In October 1936, a low right cervical node developed. Aspiration biopsy showed carcinoma. This grew rapidly and invaded the sternomastoid tendon. Radiation gave temporary arrest. In late 1937 the patient died, with the primary lesion controlled, but with extensive metastases.

CASE 4: A 41-year-old woman had basal-cell carcinoma of the right auricle, recurrent after operation. In 1942 a basal-cell tumor in the lower half of the helix had been excised. There was recurrence in 1944 and reexcision had been carried out. In 1946 there was recurrence at the inferior edge of a 4 cm.-long defect in the helix. Radiation therapy was given in November 1946—12 doses of 500 r each to a field from 3 cm. in diameter down to 2.7 x 2 cm., using 140 KV, HVL 4 Al, at 15 cm. distance. The lesion has been in arrest to date.

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To the various surgeons, internists and others who kindly referred patients for consultation or treatment, the authors are deeply indebted—as they are to the residents in radiology who assisted with the treatment and aftercare of the hospital patients.

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The Distribution of Coccidioidomycosis in Southern California

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SUMMARY

In coccidioidin skin test surveys among persons of high school age in Saugus, Canoga Park, Banning and Palm Springs areas the average incidence of positive reaction was 15 per cent. Although considerably less than the 68 per cent incidence reported among high school students of Kern County, it is high enough to indicate pockets of relatively high endemicity in Southern California below the San Joaquin Valley.

Histoplasmin tests were performed on most of the persons tested with coccidioidin in this survey. The over-all incidence of positive reaction in the group was 7.6 per cent. Most of the subjects with positive reaction to histoplasmin gave a history of having previously lived in some area in the central United States where histoplasmosis is known to be endemic.

A few subjects who had positive reaction to coccidioidin tests and who had lived in areas known to be endemic for coccidioidomycosis but not for histoplasmosis, also had positive reaction to histoplasmin. However, the induration produced was always smaller than that caused by the coccidioidin reaction, and there was minimal confusion in interpreting the tests.

FOR years it was assumed that coccidioidomycosis was acquired almost exclusively in the San Joaquin Valley of California; hence the use of its common colloquial name, "San Joaquin Valley Fever." Other parts of the Pacific Southwest of the United States[1, 3, 6, 9, 10] eventually were recognized to be endemic areas and in 1943 the Office of the Surgeon General, U. S. Army, prepared a distribution map of the known and suspected areas of coccidioidomycosis. In that map, the region of California south of the San Joaquin Valley was depicted only as an "area of suspected endemicity." Subsequent reports of infection of armed forces personnel[18, 20, 22] showed that coccidioidomycosis occurred in several widely distributed areas of that region.

From the Pathology Laboratory, Los Angeles County General Hospital and Department of Microbiology, School of Medicine, University of Southern California, Los Angeles. Aided by a grant from the Research Fund, Los Angeles County Hospital Attending Staff Association and by a contribution to the Bacteriology Research Fund, University of Southern California, by Mr. Lewis S. Rosenstiel.

During the Second World War the microbiology laboratory of the Los Angeles County General Hospital was requested to cooperate with certain of the military units in laboratory and epidemiologic studies on coccidioidomycosis. Reports of certain of these were made available through the courtesy of Dr. George A. Young, Jr., then with the California-Arizona Maneuver Area, and those data which apply to the southern part of California are included in the distribution map of this report.

After Willett and Weiss[22] reported that 83 cases of coccidioidomycosis developed near Banning, California, the laboratory subsequently performed coccidioidin test surveys in the high schools of Banning and Palm Springs in order to determine whether there was an unusually high incidence of positive reaction among the young adults of these related areas.

Los Angeles County General Hospital records showed that a few patients with coccidioidomycosis had been admitted to the hospital from surrounding counties. These led to a study of the records of coccidioidomycosis in county hospitals of those counties in order to determine whether such cases had without doubt originated in the counties. Reports of cases from Santa Barbara, Ventura, Los Angeles, Orange, Riverside, San Bernardino, and San Diego counties were verified and are included in this study.

Los Angeles County General Hospital records also indicated that cases had originated near Canoga Park in the San Fernando Valley and suggested this region as an endemic focus. Seven patients with coccidioidomycosis[11] were subsequently admitted to the Los Angeles County General Hospital in the fall of 1948 from a Los Angeles County probation camp near Saugus, which is 12 miles north of San Fernando.

These observations led to the organization of serial skin test and serial complement fixation test surveys in three probation camps within the county, and also to coccidioidin test surveys in Canoga Park and Newhall high schools. A similar survey in Los Angeles High School, located within the city of Los Angeles, was organized as a control.

This report, therefore, includes information on coccidioidomycosis derived from the following sources: (1) Certain reports among the armed forces stationed in southern California during the Second World War; (2) reports of cases from county hospital records in Southern California or from

physicians within the area, these reports having been checked to determine whether or not the patient was a permanent resident of the area; (3) an outbreak of coccidioidomycosis in a Los Angeles County probation camp near Saugus, together with serial skin test surveys made in this camp and in two other camps within the county; (4) skin test surveys in five different high schools within the area (see map and Table 1).

Recent reports in the medical literature[2,5,16,17,21] on the distribution of histoplasmosis as based on histoplasmin surveys and questions relating to the specificity of the coccidioidin and histoplasmin reactions suggested the desirability of performing histoplasmin tests. These were performed on 984 of the individuals tested in the course of this study (see Table 2).

The histoplasmin used was from Lot H3 prepared by Dr. C. W. Emmons of the National Institutes of Health, and was furnished through the courtesy of Dr. C. E. Palmer. It was used in a dilution of 1:1,000.

The coccidioidin was from Lot A1 prepared in the Los Angeles County Hospital Laboratory by methods described by Kessel and co-workers.[10] It was used in a dilution of 1:100.

One-tenth cubic centimeter of each antigen was injected intracutaneously into the flexor surface of the forearm, and the results were observed 48 hours after injection. The results were scaled as follows:

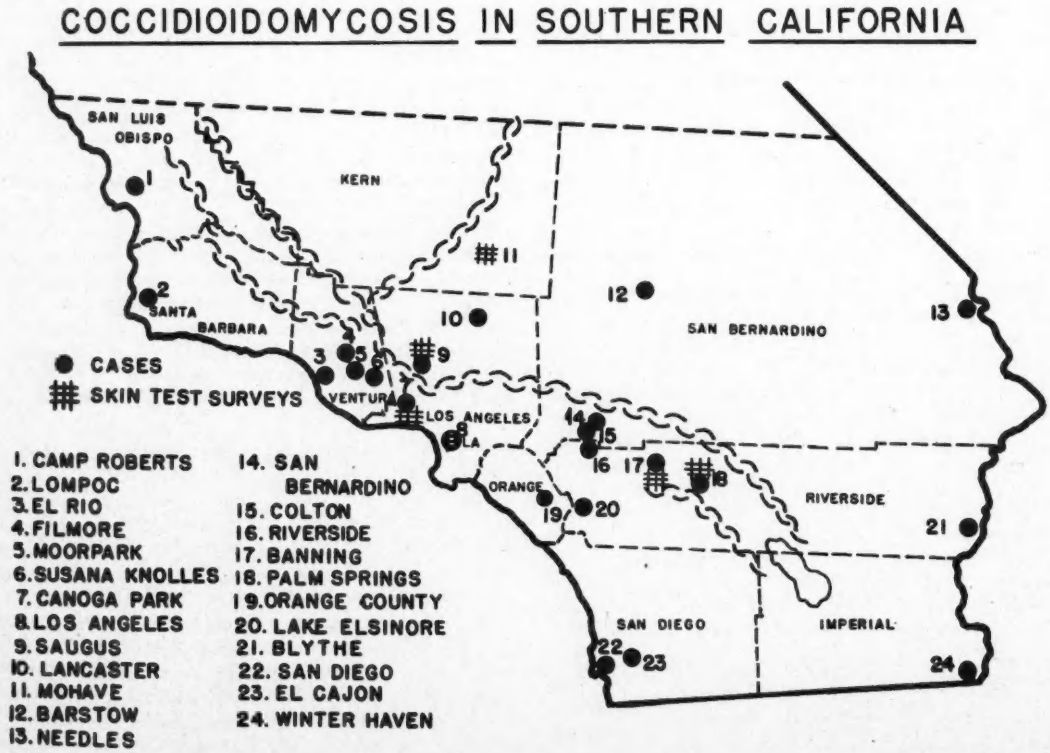
1+, = 5 to 9 mm. induration
2+, = 10 to 14 mm. induration
3+, = 15 or more mm. induration
4+, = 15 or more mm. induration plus necrosis.
Erythema alone was not regarded as a positive reaction.

RESULTS AND DISCUSSION

Coccidioidomycosis

The results of the coccidioidin surveys are summarized in Table 1. Of the 1,058 persons tested, 122 (11.5 per cent) had positive reaction. The range for the groups tested varied from 4 per cent in the Los Angeles High School to 20 per cent in the Banning and Palm Springs high schools. Since it was desired to determine the incidence of coccidioidin reactors who had acquired sensitivity in each area studied, careful histories of past and current residence in areas previously established for either coccidioidomycosis or histoplasmosis were taken from each one tested.

The persons tested were separated into two groups (Table 1), one group comprising those with previous residence in an area in which coccidioidomycosis was endemic, the other comprising those who had not resided in a known endemic area. "Residence," in this presentation, indicates residence of more than one month in a known endemic area. A majority of the reactors had resided at some time in areas previously recognized to be endemic; in this



group, the lowest percentage of positive reactors in any of the seven areas in which tests were conducted was 16 (probation camp, Azusa) and the highest was 30 (Newhall High School). In the other group, the range was from no positive reactors in one of the seven areas to 17 per cent in another.

It is assumed that there is little or no endemic coccidioidomycosis in the areas in which there was low incidence of positive reaction to coccidioidin tests. On the other hand, the three areas in which the highest incidence of positive reaction was recorded—the average for the three was 15 per cent —may be considered as newly recognized endemic areas. These are the Banning-Palm Springs area in which Willett and Weiss[22] reported 83 cases of coccidioidomycosis; Camp 4 near Saugus, from which seven patients with the disease were admitted to the Los Angeles County General Hospital in October 1948;[11] and Canoga Park, in the San Fernando Valley where several patients were suspected to have become infected. The average incidence of positive reactions (15 per cent) in the three newly recognized areas of endemicity in Southern California compares with an incidence of 68 per cent reported by Gifford[8] in similar age groups in Kern County high schools.

It is of particular interest to compare the low percentage found in the Los Angeles High School students with the higher percentages in the other high school groups. For the entire group of Los Angeles High School students tested, the incidence of positive reactions was 4 per cent, and it was only 1.6 per cent for those who were not aware of having lived in areas known to be endemic for coccidioidomycosis. The Los Angeles High School is in the center of the City of Los Angeles, and the students may be cited as a satisfactory control group, since they have a minimum opportunity for exposure to dust containing arthrospores of Coccidioides immitis. Such opportunity would be afforded only by occasional trips to known endemic areas or by exposure to arthrospores brought to Los Angeles from known endemic areas in dust, in cars, clothing or other objects. Reports in the past have shown that coccidioides may be transferred in this manner.

Distribution Map

In the past, the tendency in reporting mycotic diseases has often been to indicate the area where an infection was diagnosed or where the sensitivity of a patient was observed, without regard to his past residential history. This may lead to an entirely erroneous impression regarding geographical distribution of a disease, since the infection may have been acquired in a region quite remote from the one where the case was reported. In the accompanying map the cases of the disease and the sensitivity causing positive reaction to skin test were verified to have been acquired in the areas marked.

Evidence from these sources, together with reports of cases in military personnel stationed in the same geographic areas during and since the Second World War, shows that infections may be acquired in the following Southern California counties: Kern, southeast of Tehachapi,[18] San Luis Obispo,[20] Santa Barbara,[19] Ventura, Los Angeles,[11] Orange, Riverside,*[22] San Bernardino,* San Diego,[13-15] and Imperial.* These data point to a wide distribution of Coccidioides immitis in the southern part of California, and the map is not presumed to be complete. The cases reported to date also indicate that isolated pockets or areas of high infection rate may exist interspersed with areas of low endemicity.

Histoplasmin Surveys

The histoplasmin tests made in this study are summarized in Table 2. Of 984 persons tested, 75 (7.6 per cent) had positive reactions. These reactors were divided into two groups—those in Group 1 having previously resided in a known histoplasmosis area as judged by the map prepared by Smith and co-workers,[21] and those in Group 2 never having resided in an area in which histoplasmosis is known to occur. There was pronounced difference in incidence of reactions between the two groups. In Group 1 the percentage of positive reactors ranged from 14 per cent in the Los Angeles High School group to 45 per cent in Camp 5. In Group 2 there were few who had positive reaction to histoplasmin,

*Endemicity in Areas 13, 21 and 24 (on the map) was reported by the California-Arizona Maneuver Area.

TABLE 1.—*Coccidioidin Surveys in Southern California Areas*

Area	Total No. Tested	Total No. Positive	Per Cent Positive	Prev. Residence in Coccid. Area		No Residence in Known Coccid. Area	
				No.	Per Cent+	No.	Per Cent+
Probation Camps:							
No. 4 Saugus	100	14	14	31	20	69	12
No. 3 Calabasas	78	6	8	25	25	53	0
No. 5 Azusa	60	4	7	27	14	33	3
High Schools:							
Banning and Palm Springs	74	15	20	21	21	53	17
Canoga Park	441	65	15	82	24	359	13
Newhall	85	9	11	20	30	65	5
Los Angeles	220	9	4	38	16	182	1.6
Total	1,058	122	11.5				

with the range from zero to 4 per cent. Most of those tested in this Southern California survey who had positive reaction to histoplasmin, had previously lived in areas reported to be endemic for histoplasmosis. A related observation is that in the three clinical cases of histoplasmosis reported in the literature as occurring in California, the patients had previously lived in Louisiana,[4] Tennessee,[12] and Nebraska,[14] respectively.

Such observations further illustrate the importance, in epidemiologic studies, of ascertaining the previous residences of patients before the geographic origin of a given case is assigned.

Double Reactions

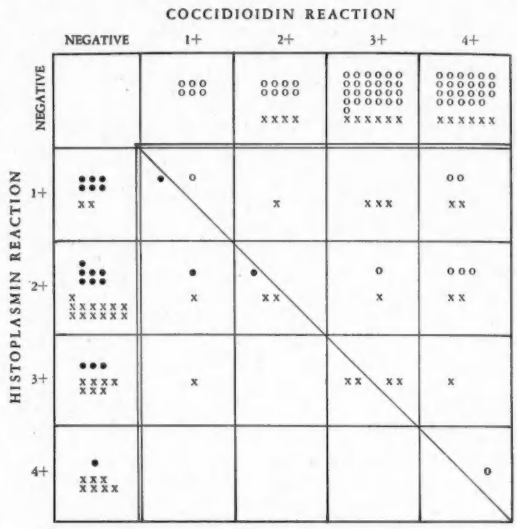
Chart 1 shows the intensity of reaction to coccidioidin and histoplasmin in 153 cases in relation to the residence history of the subjects tested.

In the chart it may be noted that: (1) The 78 cases in which there was positive reaction to coccidioidin alone are distributed in the top squares—six with 1+ reaction, eight with 2+, 25 with 3+ and 23 with 4+. (2) The 46 cases in which there was positive reaction to histoplasmin alone are distributed in the left hand squares. (3) The 29 cases in which there was positive reaction to both tests are scattered among the remaining 16 squares of the table.

Of the 29 persons with reaction to both coccidioidin and histoplasmin, 18 had lived in both coccidioidomycosis and histoplasmosis areas, three had lived in histoplasmosis areas and eight had lived only in coccidioidomycosis areas. The three who had previously lived solely in histoplasmosis areas but now live in Southern California are likely to have passed through an area in which coccidioidomycosis is prevalent—Arizona or the San Joaquin Valley—in order to reach the southern part of California. Therefore, possibility of sensitization to coccidioides en route to Southern California cannot be excluded. For this reason, no attempt is made to evaluate the cross-reactions in this group of persons. Cross-reactions in persons from histoplasmosis areas can best be studied in subjects who have never travelled in an area in which coccidioides is known to be present.

With regard to the eight persons who had lived only in coccidioidomycosis areas, yet had positive reaction to histoplasmin as well as to coccidioidin,

Chart 1.—Graph Showing Residence Histories of Coccidioidin and Histoplasmin Reactors and Relative Severity of Reactions



O Residence in coccidioidomycosis areas only.

X Residence in both coccidioidomycosis and histoplasmosis areas.

● Residence in histoplasmosis areas and travelled through coccidioidomycosis areas.

this should be noted: In six of the eight cases, the reaction to histoplasmin was of different degree than the reaction to coccidioidin; and even in the two cases in which the degree of reaction for the two tests was nominally the same (at 1+ in one instance and 4+ in the other) actually the exact size of the area of induration caused by histoplasmin was smaller than that caused by coccidioidin. There were, therefore, no cases in this series in which identical intensity of the reaction might have led to confusion in reading test results.

Question arises as to why cross-reactions between coccidioidin and histoplasmin occur. Three explanations may be considered. One possibility is that a common sensitivity occurs. (Assuming that is true, it was demonstrable in eight cases in the series reviewed.) Another possibility is that *histoplasma capsulatum* exists to a limited extent in the areas in question and some persons become sensitized to

TABLE 2.—*Histoplasmin Surveys in Southern California Areas*

Area	Total No. Tested	Total No. Positive	Per Cent Positive	Prev. Residence in Histo. Area		No Residence in Known Histo. Area	
				No.	Per Cent +	No.	Per Cent +
Camp No. 4	100	9	9	21	25	79	2.5
Camp No. 3	78	8	10	24	25	54	4.0
Camp No. 5	60	5	8	11	45	49	0.0
Canoga Park	441	30	7	164	17	277	0.7
Newhall	85	11	13.0	28	32	57	4.0
Los Angeles	220	12	6	86	14	124	0.0
Total	984	75	7.6				

this specific antigen. A third possibility is that some other fungus in the area induces intradermal sensitivity to histoplasmin. The latter two possibilities can be determined only by future investigation, and at present only the first suggestion will be reviewed.

Emmons[7] in animal experiments observed that two out of seven guinea pigs infected with Coccidioides immitis gave positive reactions when tested with histoplasmin. Of ten animals inoculated with Coccidioides immitis in a study by the authors, two had slight histoplasmin reaction. Since the cross-reactions both in experimental animals and in man observed in these studies are consistently less severe than the reaction with the specific or homologous antigen, there is little danger of confusion in reading the test. Smith and co-workers also drew this conclusion, although they left the impression that cross-reactions between coccidioidin and histoplasmin occur in a considerably higher percentage of persons than was observed in this study. They did not, however, give the previous residential histories of the persons tested. In fact, they stated, "Of course, one asks if these reactions to histoplasmin might not have been the results of independently acquired sensitivity to histoplasmin. In most instances this possibility could not be excluded." They did, however, cite 31 cases of coccidioidomycosis in which, prior to the onset of symptoms, the patients had negative reaction to both coccidioidin and histoplasmin. In this group, all patients subsequently had positive reaction to both coccidioidin and histoplasmin. In correspondence concerning the differences in incidence observed in the two different surveys, Dr. Smith suggested that the variable results may lie in differences in the histoplasmin used.

In the Los Angeles County Hospital 15 patients with proven active coccidioidomycosis recently were tested with both coccidioidin and histoplasmin. Five were tested with Lot H3 histoplasmin used in the survey herein reported, and ten with Lot H40 procured from Dr. E. S. Weiss and used in a dilution of 1:500. None of the 15 patients had previously lived in a known histoplasmosis area. All had positive reaction to coccidioidin and none had a positive reaction to histoplasmin. This observation further supports the thesis that minimal confusion occurs in the differentiation of coccidioidin and histoplasmin reactions.

The authors wish to express their appreciation to the following for their cooperation in procuring data used in this report: Dr. H. A. Ball, pathologist, San Diego County Hospital; Dr. J. P. Blanchard, pathologist, Santa Barbara County Hospital; Mr. Lester C. Dalbey, principal, Wm. S. Hart Union High School at Newhall; Dr. Warren Fox, health officer, Riverside County, and cooperating staff members of Banning and Palm Springs high schools; Dr. Roy O. Gilbert, director, Los Angeles County Health Department, and staff of the Division of Epidemiology and of the San Fernando District; Dr. J. D. Kirshbaum, pathologist, San Bernardino County Hospital; Dr. J. J. Montanus, pathologist, Orange County Hospital; Dr. G. Wendell Olson, Fullerton; Dr. C. M. Sellery, director, Health Services Branch, Los Angeles City Schools, and the cooperating staff members of the Los Angeles and Canoga Park high schools; Dr. H. D. Stalley, superintendent, Riverside County Hospital; Dr. C. T. Steggal, resident, Ventura County Hospital; Mr. John Zuck, director, Los Angeles County Probation Department, and his staff.

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Therapy of Parkinson's Disease

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SUMMARY

The most disabling form of Parkinsonism is that occurring after encephalitis. It may occur in persons of any age. The results of surgical treatment, which has been used for the most part only for seriously handicapped patients, have been discouraging in general, although in a few isolated circumstances operation has been of dramatic benefit.

The solanaceous alkaloids—atropine, stramonium and hyoscine—either in pure forms or in mixed extracts or tinctures — are the best established drugs at present for the treatment of the postencephalitic forms of Parkinsonism. They have not proven too helpful for patients in the older age group with paralysis agitans. The antibistaminic compounds, particularly Benadryl,® have been a very valuable addition. They are of greatest value for patients in the older age group. The newer synthetic compounds, Artane® and Panparnit,® are also valuable additions. Amphetamine and the related and subsequently produced agents in this group are very helpful for patients showing undue fatigue and lethargy. Tolserol® is proving helpful, particularly for patients with painful spasms of rigid muscles.

IN a review of the literature it was noted that paralysis agitans of the degenerative or arteriosclerotic type appearing late in life seemed to be most commonly commented upon.

Beginning in 1917, just 100 years after James Parkinson had described the disease as a syndrome, and particularly during the winters of 1918 through 1920, serious attacks of epidemic encephalitis occurred. Following this pandemic numerous manifestations of a syndrome resembling paralysis agitans occurred. This latter syndrome is now referred to as postencephalitic Parkinsonism. The postencephalitic form differs from the classic description by Parkinson in that persons of any age may be affected and there are many associated symptoms which make the condition more disabling. Most investigators[7, 10] consider paralysis agitans and Parkinsonism as synonymous and group them under three general headings: Postencephalitic, idiopathic, and arteriosclerotic. The syndrome is occasionally observed in toxic, neoplastic or post-traumatic states. While rare, these conditions must be considered in differential diagnosis.

Basically the disease is an involvement of the extrapyramidal portion of the central nervous system.[3, 4, 5] It varies in intensity and extent throughout the structures of this system. Owing to lack of knowledge of the anatomy and physiology of the structures, the pathophysiological disturbances of this disease cannot be concisely explained. The most common sites of pathologic change are the globus pallidus, the putamen and the substantia nigra. The cortex is less frequently involved, and the corpus Luysii and the red nuclei only occasionally. Recent investigators have been directing their attention to the reticular substance, and in all probability this latter locus will prove to be an important area for study and understanding.

The commonly observed signs are: Increased muscle tonus (rigidity), tremor of rest, flexed posture and festination of gait—the classical picture of paralysis agitans. Persons with the postencephalitic form of the disease have, in addition, increased salivation, oily skin, oculogyric crisis, and reversals of sleep rhythms. Psychic disturbances occur and must be considered in all therapeutic programs. As in all chronic illnesses, discouragement and depression are common. The psychic symptoms at times become very distressing or disabling. This is particularly true in younger persons in whom behavior disorders are often the only evidence of the disease. As the patient's intellect is seldom affected, psychotherapy is important.

Parkinsonism can be classified as mild, intermediate or severe. In the mild cases, quite often the patient is more comfortable on a good hygienic regimen than with medication. The side-reactions accompanying the use of drugs are quite often so distressing that the patient with mild Parkinsonism would prefer getting along without drugs. The greatest opportunity to aid with medication exists in the intermediate group.

TREATMENT

The first attack upon this problem should therefore be directed toward psychic rehabilitation and maintaining physical strength and vigor in the patient. It is wise to avoid terms alarming to the patient—terms such as "shaking paralysis," "creeping paralysis," and "sleeping sickness." It is far better to emphasize the slowness of progression of the disease and to reassure the patient in any possible manner. Often this entails a reordering of the patient's life. As mental or physical fatigue intensifies the symptoms, activities should be planned accordingly. There should be a moderate amount of

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outdoor activity. As the rigid muscles respond to heat, physiotherapy in the form of baking and massage is indicated. For patients with muscle spasm, a warm bath before retiring may be helpful.

The postencephalitic form is a sequel to epidemic encephalitis. It may, but rarely does, follow other forms of encephalitis. As knowledge of the anatomy and physiology of the nervous system has developed, surgical approaches to the problem have been made. Areas 6 and 4S have come under scrutiny and some investigators have ablated these areas. At first the results were promising, but in most instances the symptoms returned after recovery from the initial shock of operation. Other areas and tracts have been ablated, with questionable results. Perhaps the greatest surgical success has been achieved in relief of postencephalitic hyperpnea;[8] section of the phrenic nerve relieved the distressing symptoms and restored totally incapacitated patients to reasonable comfort. With an increase of knowledge in the field of neurophysiology as pertains to the extrapyramidal system, it is probable that neurosurgeons will devise means more suited to individual cases. Certainly, attempting surgical relief in severe cases is justified, and the information thereby obtained may permit more rapid advance in all fields of therapy. At present, palliative treatment is about all that is available for the patient with severe Parkinsonism.

The antispasmodic drugs of the solanaceous alkaloids[9] have been, and probably remain, the most useful therapeutic agents. The main alkaloids used are atropine, scopolamine, and stramonium. The early investigators tended to use small doses, but with more experience it was found that massive dosage was necessary. In mild cases the side-effect of mydriasis and the drying up of the saliva was more distressing than the moderate muscular rigidity. It was observed that patients with intermediate Parkinsonism had considerable tolerance for these drugs. With the alkaloids, a minimal dose should be used at first and the dosage then increased to the point of therapeutic results or the patient's tolerance. The response of a patient to an antispasmodic drug may vary from time to time. This does not appear to be ascribable to tolerance or addiction, but rather to variations in the physiological status of the patient. The psychological benefit of changing medication is occasionally the explanation. The older tinctures and extracts were variable in potency. White wine extract has produced a more constant and therapeutically effective drug. There are several satisfactory preparations available.[2, 6, 9] Vinobel® and Rabellon® are examples. Hyoscine hydrobromide, in 0.4 and 0.6 mg. doses, three to 12 times per day, is very helpful to most patients. The greatest usefulness of this drug is in the control of oculogyric crisis. For emphasis: Therapy must be tailored to the peculiar needs of each patient and must be altered as the needs change.

Quite often patients complain of undue drowsiness, a distressing symptom of this disease. With the advent of sympathomimetic drugs (ephedrine, amphetamine),[2] it was realized that they were logical additions to the therapeutic program of these patients. From 10 to 25 mg. of amphetamine is usually given at the time the patient rises in the morning, and if necessary it is repeated around 11 a.m. It is advisable not to give this drug in the afternoon as it may interfere with sleep at night.

Thus, the alkaloids and sympathomimetic drugs constitute the pharmacological armamentarium for the treatment of this disease. The recent chemical synthesis of drugs offering better control of symptoms is a most encouraging development.

ANTIHISTAMINIC DRUGS

Benadryl,® an antihistaminic, was tried empirically by Budnitz[1] in September 1946. The results were most encouraging. Since then, various other forms of antihistaminics have been tested. In the author's experience Benadryl has proven the drug of choice. It has been most useful for patients with paralysis agitans—relaxing the tonus, reducing the tremor and drying the saliva. The alkaloids, added to the regimen, increased the benefit. Twelve patients with severe paralysis agitans were given Benadryl with alkaloids. Tonus was reduced in each case; tremor was arrested in two and reduced in eight. All the patients showed improvement in that they developed a sense of well-being. In postencephalitic patients, salivation was controlled, emotional expression improved in facial muscles, and a renewed interest in activities was noted by relatives. Benadryl is administered in 50 mg. doses, three to four times per day. The dosage of alkaloids can be reduced gradually as the patient is started on the antihistaminic.

Corbin[2] commented upon the use of a new synthetic antispasmodic agent, Artane.® The pharmacological properties of this compound have been carefully studied. It is supplied in 2 mg. tablets provided with a line for halving the dose. Most patients can tolerate a 2 mg. tablet three times a day. It is usually administered before meals and the dose gradually increased to four or five 2 mg. tablets a day. Uncomfortable side-effects are few and patients who have tolerated high atropine alkaloid doses may be given up to 10 or 15 mg. of Artane a day. The symptoms of toxic effect were reported as minor. Usually these consisted of a feeling of giddiness, unsteadiness of gait, blurring of vision, dryness of the mouth, and occasionally nausea, nervousness and tinnitus. Some patients became extremely nervous and it was reported that two patients had mild delirium. The two patients who had the most pronounced side-effects had a history of sensitivity to other drugs. In cases in which side-effects developed, use of low dosage and building up to tolerance permitted continuance of the drug. Corbin stated that the feeling of nervousness caused by Artane in some cases was controlled by the administration of phenobarbital. It has been the author's experience that most postencephalitic patients do not tolerate sedative drugs well, and for that reason changing to some other therapeutic agent is suggested.

Tolserol®[4,5] is a more recently introduced therapeutic agent which has pronounced spasmolytic effect. Its greatest usefulness is in cases in which muscle spasm and pain are present, or in which dystonic or athetoid movements are complicating factors. This drug is available in four forms: Tablet, capsule, elixir and 2 per cent solution for intravenous use. It is usually administered in doses of 1 gm., three to four times a day. The liquid form is absorbed more rapidly and has proven more satisfactory in the author's experience. The intravenous administration of Tolserol produces a rapid therapeutic level of the drug, and results can be determined in a short period of time.

In 1946, Domenjoz[3] reported pharmacological experiments with a variety of synthetic compounds related to Trasentin® and found that they had approximately one-tenth the antisecretory effect of atropine and yet were powerful antispasmodics. The least toxic and most efficient of these was Panparnit® (introduced under the name of Parpanit®). It is related to atropine and hyoscine in structural formula. Schwab and Leigh[7] reported on this drug. Their work was well controlled, the results well validated, and the action upon muscles determined by electromyelography. The drug is available in a 12.5 mg. tablet and a 50 mg. tablet. It is advised that the drug be given on the following schedule: One 12.5 mg. tablet every three to four hours for five doses during the first day, two 12.5 mg. tablets five times on the second day, three 12.5 mg. tablets five times on the third day, then, beginning on the fourth day, one 50 mg. tablet five times a day. The dosage then may be adjusted up or down according to the patient's needs. Most patients seemingly are benefited on the 50 mg. tablet regimen. It is important to note that the drug is utilized rapidly in the body, and therefore must be administered at three- to four-hour intervals to get maximum results.

When using any of the newer drugs, the alkaloids should be continued. A gradual reduction should be carried out. In many cases the patient is most comfortable if a combination of drugs is continued.

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The Diagnosis and Treatment of Meningitis

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SUMMARY

Treatment of meningitis is no longer a question of the administration of antimeningococcal serum and awaiting results. Today there is at hand an ever expanding armamentarium of drugs effective on various bacteria, rickettsia and some of the larger viruses. The skillful use of these singly or in combination offers an excellent prognosis in most forms of bacterial meningitis. Tuberculous meningitis continues to present a poor outlook, but this has been improved with more intensive therapy. More effective agents are needed in the treatment of this disease.

"Shotgun" therapy may be indicated in critically ill patients prior to accurate bacteriological diagnosis; it is more important that therapy should include an effective agent or combination of agents than to attempt to determine in advance the most potent form of specific therapy. Partially treated purulent meningitis may be confused with aseptic meningitis. There is at present no effective therapeutic agent for the viral meningitides, but the prognosis is favorable in most of these diseases without specific therapy.

DIAGNOSIS is so intimately a part of the treatment of meningitis that the two must be considered together. A review of the disease entities which raise the suspicion of central nervous system disease will aid in consideration of specific treatment.

First in order are diseases which give rise to stiffness of the neck but in which there is no evidence of meningeal reaction or of cellular response or pleocytosis of the cerebrospinal fluid. Patients with such symptoms are frequently referred to a communicable disease unit with a diagnosis of meningitis or poliomyelitis. If pleocytosis is absent, then it is probable that the neck stiffness is caused by either extraneural disease of the head and neck or systemic disease such as bacteremia, pneumonia, pyelitis, or exanthemata. Among the extraneural causes of the symptom are trauma, tumors in the cervical region, and infections of the upper respiratory tract including the associated structures (pharyngitis, sinusitis, otitis media and cervical adenitis). Poliomyelitis will sometimes cause typical symptoms and course without provoking pleocytosis. When the stiffness of the neck is of extraneural origin, pain may interfere with any movement of the head and neck, whereas the patient with meningeal irritation usually retains all movement but flexion. Frequently, a patient with "wry neck" can flex his neck even though he cannot extend or rotate it. The signs of meningeal irritation caused by systemic infections probably are a result of actual irritation of the meningeal vessels. Bacteremia, viremia, or toxemia may provoke nuchal rigidity because of injury to meningeal vessels without pleocytosis or other evidence of actual meningeal infection. The term "meningismus" should be applied only to those cases in which actual invasion of the meninges by a pathogenic organism can be excluded. Disease of the upper respiratory tract may give rise to toxemia and meningismus in addition to local inflammatory reaction.

If the cerebrospinal fluid contains over five leukocytes or any polymorphonuclear leukocytes per cu. mm. (that is, cerebrospinal fluid pleocytosis), then meningitis in the sense of inflammatory response exists, although there is still a possibility that no infectious agent has gained entry. Tumors of the brain and brain stem, heavy metal intoxications, and so-called "neighborhood reactions" must be considered. Neighborhood reactions may arise from conditions such as abscess of the brain or of the lateral sinus. Extension of these processes into the cerebrospinal fluid by rupture of the intervening wall may convert them to frank purulent meningitides.

Hemorrhage may be confused with meningitis. In the presence of neck stiffness and coma, lumbar puncture may be necessary for purposes of differentiation. Although gross blood in the spinal fluid usually confirms the diagnosis of subarachnoid hemorrhage, in some cases there is blood in the spinal fluid of a patient with meningitis. Differentiation is made by counting both the leukocytes and the erythrocytes per cu. mm. of spinal fluid. In cerebral hemorrhage, the leukocytes are present in the same ratio to the erythrocytes as exists in the peripheral blood; in meningitis the number of leukocytes far exceeds the number accounted for in this manner.

If spinal fluid pleocytosis exists and no obvious non-infectious cause can be determined, then it must be assumed that an infectious agent is responsible. There are two main subgroups—infections by bacteria or other larger organisms and infections attributable to viruses or to virus-like agents. These are usually referred to, respectively, as purulent and aseptic meningitides. (More correctly, there should

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be included another classification, serous meningitis, in which there is less pleocytosis than in purulent meningitis; but this term is used for a specific form of tuberculous meningitis which will be referred to later.)

Meningococcal meningitis. Typically, in meningococcal meningitis, pronounced limitation of neck flexion develops in the course of a febrile illness of variable severity. Prostration may be mild or severe. Headache, fever, nausea, vomiting, restlessness, irritability, convulsions, coma, signs of cerebral irritation and increased intracranial pressure may vary widely. Especially in infancy, the evidence of central nervous system disease may be most meager. The presence of a hemorrhagic cutaneous eruption associated with meningeal irritative signs often proclaims the diagnosis. Associated rashes may be nondescript, morbilliform or urticarial and *not* of equal diagnostic significance.

The blood has a high polymorphonuclear cell content with a preponderance of immature forms and absence of eosinophils. Fluid removed at lumbar puncture is often milky white with over a thousand leukocytes—primarily polymorphonuclear—per cu. mm. Chemically, the fluid is abnormally high in protein content and low in sugar.

Bacteriological confirmation of the diagnosis rests on the demonstration of intracellular, Gram-negative diplococci in a smear of the spun sediment and/or in suitable culture media. Often the organisms are not observed on the direct smear—in fact, of all forms of bacteria causing meningitis, the meningococcus is most frequently *not* detected by direct smears or even by cultures, particularly if even minimal specific therapy has been given. However, this interference with the demonstration of organisms may be overcome by adding to the material to be examined or cultured an agent or agents to impair the function of antibiotics previously administered to the patient. Paraminobenzoic acid impedes the action of the sulfonamides and penicillinase inactivates penicillin. A further procedure, often successful if the organisms cannot be demonstrated on smear or regular culture, is inoculation of growing chick embryo with the fluid. Growth is rapid in this medium—positive cultures may be obtained in six to eight hours—and antibiotic inhibition of growth is minimized, presumably because of the active circulation of the embryo.

It should be stressed that even if no bacteriological evidence can be elicited the diagnosis can be established on the basis of meningitis with associated hemorrhagic rash. When these petechiae or purpuric lesions are present, smear or culture of fluid drawn from them may reveal the organisms. Occasionally, the organisms are noted by an alert laboratory technician in the smear of the peripheral blood taken for the differential cell count.

At one time[29] the specific therapy of meningitis as a whole could be covered very simply: Once the diagnosis of purulent meningitis had been made, the patient was given polyvalent anti-meningococcus serum. If he had meningococcal meningitis, he had a chance of recovering; if not, he died. A more recent recommendation,[17] that all forms of meningitis be treated with penicillin given intraspinally, equally ignores the desirability of establishing the exact cause and using an appropriate specific agent in treatment. The modern diversity of specific agents has greatly improved the over-all prognosis.

Some observers[12, 27, 28, 30] are of the opinion that sulfonamide therapy alone is sufficient in most cases of meningococcal meningitis, and it is certainly the agent of prime importance. Others give a combination of penicillin and sulfonamide preference. Aureomycin[8] appears to be effective against the organism, but Long and co-workers[25] designated it as of undetermined value. The recommended dosages are given in Table 1. If the patient is unable to take oral medication, sulfadiazine may be given by hypodermoclysis as sodium sulfadiazine in a concentration of 0.5 to 1 per cent. (A 5 per cent solution may be used, but the risk of tissue slough makes it less desirable.) This subcutaneous route gives a desirable slow continued absorption and sustained blood level rather than the abrupt rise and fall obtained by intravenous administration. It is well, particularly initially, to check the blood levels of sulfadiazine and

TABLE 1.—*Therapy of Meningococcal Meningitis*
(Agents in order of preference)

Drug	Route	Initial Dose	Daily Dose	Level (Blood or serum)	Interval (Hours)	Duration
Sulfadiazine	Oral	75 mg./kg.	150 mg./kg.	12 to 15 mg.%	4	1 week after fever
	Parenteral (Subcut.)	75 mg./kg.	150 mg./kg.	12 to 15 mg.%	8	1 week after fever
Penicillin (Crystalline G)	Parenteral (Intramusc.)	500 to 1,500 u/kg. (0.3 to 1 mg./kg.)	4,000 to 15,000 u/kg. (2.7 to 10 mg./kg.)	>0.2 u/cc.	3	1 week after fever
Penicillin (Procaine G)	Parenteral (Intramusc.)	Not recommended	Same— After disease is under control	>0.2 u/cc.	12	1 week after fever
Aureomycin	Oral	10 to 20 mg./kg.	25 to 100 mg./kg.	.....	4 to 6	1 week after fever
	Parenteral (Intraven.)	5 mg./kg.	15 mg./kg.	.....	8	1 week after fever

adjust the dosage accordingly. The level should be 12 to 15 mg. per 100 cc.

Penicillin dosage calculated on a basis of body weight leads to undertreatment of infants and children because of disproportionate urinary excretion in this age group. It does serve as a rough guide, but the actual dosage should be overgenerously calculated. Although procaine penicillin is given once daily with excellent clinical results in the treatment of many bacterial infections, in the treatment of meningitis it is preferable to maintain optimal blood levels by administering the drug at 12-hour intervals. A range of dosage has been indicated for penicillin and aureomycin. If the infection is obviously more severe the larger dose should be given.

There is now far less enthusiasm for intraspinal injection of drugs than there was formerly, largely because of the effectiveness of administration by the oral and parenteral routes, and the undesirable irritative effects of intraspinal therapy. Hoyne[18, 19] has led the objectors and seems well sustained.[13] (Probably intraspinal therapy of meningitides should be limited to the treatment of tuberculous meningitis, as will be discussed later.)

Overwhelming infection represents great toxemia and requires the use of intravenous dextrose solution, plasma, blood, and supportive agents including large amounts of adrenal extract (whether or not there is evidence of adrenal failure dependent upon adrenal hemorrhage).

Influenzal meningitis now accounts for the majority of hospital admissions for meningitis in infancy and childhood.[10, 16] (Meningococcal meningitis formerly led in this respect, but the incidence has decreased as a result of early and vigorous treatment of febrile illness.) It is primarily a disease of this age group, but does occasionally occur in adults. Usually, the infant has had a respiratory infection—frequently of several weeks' standing. Listlessness, unexplained irritability, anorexia, vomiting and/or rise in temperature may lead the physician to consider central nervous system disease. The anterior fontanelle may be bulging, but if the infant has become severely dehydrated it may be sunken. The neck may or may not be stiff. Flexion of the neck is best tested by putting the infant in a sitting position and holding something attractive on his abdomen. Attempts to force flexion of a child's neck—be he sick or well—are usually met with stubborn resistance. Almost reflex flexion following extension of the neck over the edge of a table may be helpful in totally uncooperative infants and children.

It should be stressed that the diagnosis of meningitis in infancy may rest solely on the finding of purulent cerebrospinal fluid in an infant with unexplained fever.

Grossly and chemically the cerebrospinal fluid is similar to that found in meningococcal meningitis. Smears usually reveal a pleomorphic Gram-negative bacillus which is often incorrectly recognized morphologically because of prominent bipolar granules which give it the appearance of a diplococcus. The organism may be grown on suitable culture media. Inoculation of growing chick embryo may be of value for rapid identification. Organisms from smear or culture may be more definitely identified by the capsule swelling or "quellung" reaction produced by type B antiserum. This reaction is helpful in most instances. The leukocyte count is usually elevated with a polymorphonuclear response. Culture of exudate from foci of infection such as the throat or middle ear may reveal the organism.

Therapy (Table 2) prior to the advent of aureomycin consisted of sulfadiazine, streptomycin and antiserum. Alexander[1, 2, 3] outlined a plan of therapy in which the sugar content of the spinal fluid is used as the criterion of the severity of the disease. Most other observers, including the authors, employ antiserum in cases of unusual severity, using a single dose of from 50 to 200 mg. of immune nitrogen, the size of the dose depending on a rough estimate

TABLE 2.—*Therapy of Influenzal Meningitis*
(Agents in order of preference)

Drug	Route	Initial Dose	Daily Dose	Level (Blood or serum)	Interval (Hours)	Duration
Streptomycin (Dihydro-)	Parenteral (Intramusc.)	10 to 15 mg./kg.	40 to 60 mg./kg.	.....	4 to 6	5 days
Aureomycin	Oral	10 to 20 mg./kg.	25 to 100 mg./kg.	.....	4 to 6	2 weeks after fever
	Parenteral (Intraven.)	5 mg./kg.	15 mg./kg.	.....	8	2 weeks after fever
Sulfadiazine	Oral	75 mg./kg.	150 mg./kg.	12 to 15 mg.%	4	2 weeks after fever
	Parenteral (Subcut.)	75 mg./kg.	150 mg./kg.	12 to 15 mg.%	8	2 weeks after fever
Antiserum (Type B)	Parenteral (Intraven. or intramusc.)	50 to 200 mg.	Immune Nitrogen	.....	....	Administered once in most cases

Alexander recommends:		Spinal Fluid Sugar
	25 mg. immune nitrogen	Over 40 mg.%
	50 mg. immune nitrogen	25 to 40 mg.%
	75 mg. immune nitrogen	15 to 25 mg.%
	100 mg. immune nitrogen	Under 15 mg.%

Plus intrathecal streptomycin 25-50 mg. each day for 4-5 days.

of the severity of the disease and the size of the patient. The demonstrable presence of excess antibody in the serum may be used as a guide in extreme cases in which repeated administration is required. Antiserum should be diluted in several volumes of saline and given slowly so as to avoid the possibility of severe reactions. The use of either streptomycin or antiserum intraspinally is advised by some observers,[1, 2, 3, 36, 37] considered unnecessary and injurious by others.[15, 19]

Although reports are as yet incomplete, aureomycin appears to be superior in effectiveness to streptomycin and does not present the hazard of deafness caused by injury of the eighth nerve. Long and coworkers[25] suggested the combination of aureomycin and sulfadiazine as the therapy of choice. Chloramphenicol is apparently effective in vitro and probably is equally effective in vivo. Certainly, in the severe case, aureomycin, streptomycin, sulfadiazine and antiserum may be given in combination. Streptomycin can be discontinued by the fifth day with almost complete avoidance of injury to the eighth nerve.

Supportive measures, especially the judicious administration of fluids and blood, are of particular importance in this disease in which most of the patients are infants and young children. Recently, Ingraham and Smith[26, 31] emphasized the need for exploration and surgical drainage of fluid collections in the meninges following influenzal meningitis.

Even with optimal therapy the outlook for infants under nine months of age is poor. Bloor and coworkers[4] reported a mortality rate of over 40 per cent in this age group. In those who recovered there was a striking incidence of major and minor neurological disturbances. However, in private practice and with early diagnosis the results are better; the recovery rate is 90 per cent and there are few sequelae.

Pneumococcal meningitis may occur in any age group. It is frequently secondary to sinusitis—especially that involving the sphenoid sinus—and middle ear infections. The symptoms and signs are similar to those described for meningococcal meningitis except that the patient is liable to become comatose quickly. The results of blood examination are consistent with those of acute bacterial disease. The spinal fluid is almost cream-like in consistency in many instances. Smear and culture of the spinal fluid will usually reveal the organism which can then be typed as an aid in diagnosis as well as possible therapy with type-specific antiserum. The organism may also be recovered from the blood and from foci of infection.

Penicillin is the therapeutic agent of choice, but sulfadiazine should always be given concomitantly (Table 3). The value of aureomycin[25] and chloramphenicol is as yet incompletely determined. Type-specific antisera are used infrequently. The intraspinal route of administering therapeutic agents is used less than formerly, but would seem logical in cases in which there is actual empyema of the subarachnoid space. Dowling[14] stressed the use of massive intramuscular doses of penicillin — 1,000,000 units every two hours—without intraspinal or sulfonamide therapy. Neurological complications are frequent, but the percentage of patients with no sequelae is remarkably improved since the advent of penicillin therapy. In reviewing the cases of pneumococcal meningitis treated at Children's Hospital in San Francisco, it is of interest that there has been only one death since penicillin has been used in treatment, and the patient was moribund on admission. This is particularly remarkable in view of the small doses of penicillin that were given in the first months of its use. It should be emphasized, however, that no one agent should be relied upon and that therapy should be instituted as soon as a working diagnosis is established and fluid has been obtained for study. Surgical treatment of the primary focus of infection should be carried out concomitantly when indicated.

Colon bacilli are the cause of the most common form of meningitis in the neonatal period. Infection may be associated with an abrasion, or with anatomical defects such as spina bifida or meningocele; or the portal of infection may not be apparent. In this age period, signs and symptoms may be entirely lacking or may be similar to those observed in influenzal meningitis. Frequently, the disease is not diagnosed until autopsy following a sudden, unexplained neonatal death. Meningitis should be con-

TABLE 3.—*Therapy of Pneumococcal Meningitis*
(Agents in order of preference)

Drug	Route	Initial Dose	Daily Dose	Level (Blood or serum)	Interval (Hours)	Duration
Penicillin (Crystalline G)	Parenteral (Intramusc.)	1,500 to 15,000 u/kg. (1 to 10 mg./kg.)	15,000 to 170,000 u/kg. (10 to 110 mg./kg.)	1 to 2 u/cc.	2 to 3	1 week after fever, abnormal neurological signs
Penicillin (Procaine G)	Parenteral (Intramusc.)	Not recommended	Same—After disease under control	1 to 2 u/cc.	12	1 week after fever, abnormal neurological signs
(The upper dosage is that recommended by Dowling—1,000,000 units every 2 hours in adults)						
Sulfadiazine	Oral	75 mg./kg.	150 mg./kg.	12 to 15 mg.%	4	1 week after fever, abnormal neurological signs
	Parenteral (Subcut.)	75 mg./kg.	150 mg./kg.	12 to 15 mg.%	8	

sidered a possibility in an infant with unexplained fever and irritability. The spinal fluid is similar to that in influenzal meningitis. Organisms may be found on smear and culture of the spinal fluid and on culture of the blood.

Aureomycin[25, 32] and chloramphenicol appear to be the therapeutic agents of choice in infections by E. coli. Prior to the advent of these antibiotics,[12, 19] streptomycin and sulfadiazine were used with some success.

Obviously, diagnosis in neonatal infants is a greater problem than is therapy, but continued alertness plus the prophylactic use of antibiotics when predisposing conditions are present at birth should reduce the mortality from this source. The response to therapy in infancy is not good. Even though the responsible organism may be of low virulence, the host resistance is poor and antibiotic agents have a low degree of specificity.

The Salmonella organisms, including S. typhosa, cause meningitis on rare occasions. The disease is much like that caused by the colon bacilli. It usually occurs in young infants. Therapy includes the four antibiotics referred to in discussion of the treatment of E. coli meningitis. Chloramphenicol[25, 32] seems to be more effective than aureomycin in controlling most Salmonella infections. If possible the organism should be tested for sensitivity to the various agents, but because therapy must be started immediately, this cannot be done before treatment is under way. Because of the lack of specificity, more than one agent should be employed and the effectiveness of several explored by laboratory tests and clinical observation.

Streptococci and staphylococci may cause meningitis, but the incidence has dropped sharply with the rarity of mastoiditis now that specific therapy for otitis media is available. Before the use of antibiotics, infection of the middle ear often became chronic, led to mastoiditis, then to mastoidectomy with exploration of the lateral sinus, and finally to meningitis. The beta hemolytic streptococcus and staphylococcus aureus were the major offenders.

Therapy should be massive and combined—probably sulfadiazine, penicillin,[12, 25, 32] and aureomycin should be used in combination in large doses. As previous therapy may have rendered the organism resistant to one or more of the agents, sensitivity tests should be carried out. If resistance is observed, dosage may be increased or other agents tried.

Gonococcic meningitis is rare. Penicillin[25] is the therapeutic agent of choice, but all the available antibiotics have some effect. Sensitivity tests in vitro are invaluable in planning continued therapy in severe cases.

Tuberculous meningitis is an infrequent but ominous complication of tuberculous infection. It is thought to be associated with the primary spread of the infection, but the meningeal focus may remain quiescent for an indefinite period. In support of the association with primary tuberculous disease is the observation by European workers[9, 35] that the incidence of tuberculous meningitis has decreased out of proportion to the decrease in other forms of tuberculosis following the vaccination of large segments of the population with BCG.

The onset is usually insidious; rarely fulminant. The patient complains of malaise, has low grade fever, variable headache. Eventually this progresses to pronounced lassitude and coma. At this point neurological examination reveals evidence of meningeal irritation plus palsies and abnormal reflexes which change rapidly both in intensity and location. Convulsions are frequent. Diagnosis rests on these observations coupled with knowledge of previous tuberculous infection as evidenced by positive reaction to tuberculin skin test or by clinical tuberculosis. The tuberculin skin test reaction is usually positive, but it may be negative during the early primary invasion or in the presence of overwhelming disease (the tuberculin reaction having been formerly positive.)

Results of blood studies are not remarkable except for the accelerated sedimentation rate observed in tuberculous infection. There are fewer cells in the cerebrospinal fluid—usually 200 to 300—than in the usual bacterial meningitis. At the onset there may be a preponderance of polymorphonuclear leukocytes, but as a rule most of the cells are mononuclear. A smear of the sediment will reveal tubercle bacilli in some instances, but more often the organisms are found in the coagulated protein or pellicle on the top of the tube. Culture on suitable media and guinea pig inoculation will aid in demonstration of the organisms. The chemical abnormalities in the fluid are of particular interest. As in other bacterial infections involving the cerebrospinal fluid, there is lowering of the sugar content—often of pronounced degree. This diminution in sugar content is felt to be caused by the metabolic activity of the infecting organisms. Concomitant reduction in chloride content is usually noted and cannot be explained on the same basis. Perhaps the so-called "blood-brain barrier" is altered, resulting in spinal fluid chloride values that approximate the 100 mEq. per liter normal of blood rather than the 120 mEq. per liter normal of cerebrospinal fluid. Cerebrospinal fluid chloride content less than 105 mEq. per liter or 600 mg. per 100 cc. should be considered almost diagnostic of tuberculous meningitis.[20] The cerebrospinal fluid protein content is increased. Sometimes there is pleocytosis without other evidence of infection. The disease in such cases is referred to as "serous" meningitis, for which the prognosis is much better than it is for the usual form of tuberculous meningitis. The cause may be a form of "neighborhood" reaction in which tuberculous foci lie adjacent to the meninges.

To date, the most successful antibiotic for tuberculous meningitis is streptomycin.[6, 7, 11, 22, 23, 24, 33] This must be given intramuscularly and intraspinally. Dosage schedules are shown in Table 4. Even though with this dosage—4 gm. a day for the average adult — there is a great risk of deafness and

TABLE 4.—*Therapy of Tuberculous Meningitis*
(Agents in order of preference)

Drug	Route	Initial Dose	Daily Dose	Level (Blood or serum)	Interval (Hours)	Duration (Months)
Streptomycin (Dihydro-)	Parenteral (Intramusc.) (Intraspinal)	15 mg./kg.	60+ mg./kg. 50 to 100 mg.	....	4 to 6 24	2 to 6 1 to 3
Promizole	Oral	.....	1 to 8 gm. Gradual increase	1 to 3 mg.%	6	12 to 36
Paramino-Salicylic Acid	Oral	.....	10 to 15 gm.	.....	6	12 to 36

ataxia, the high mortality rate if smaller amounts of the drug are used makes this risk necessary. Dihydrostreptomycin has largely supplanted streptomycin, but damage to the eighth nerve still occurs in a significant percentage of cases. Promizole, paramino salicylic acid[5, 6, 7, 11, 22, 23, 24, 33] and other agents are sometimes used in conjunction with streptomycin with apparent benefit. Supportive measures are as important in management of tuberculous meningitis as they are in tuberculous infection generally and should not be overlooked in the pursuance of antibiotic regimens. Lincoln[22] stressed that the disease may progress even to coma during treatment, yet the patient recover. Lincoln,[6, 7, 11, 22, 23, 24, 33] DeBré and others report arrest of tuberculous meningitis in children in from 40 per cent to 70 per cent of cases. Results with adults are far less encouraging.

Fungi and molds cause meningitis rarely. Clinically, disease of the meninges caused by these agents is much like tuberculous meningitis. All available antibiotics have been used in treatment, with variable but inconspicuous success.

Aseptic Meningitides

A large number of disease entities of varying etiologic delineation are included among the aseptic meningitides. The common denominator is spinal fluid pleocytosis, with the number of cells varying from a few to a thousand or more. No bacteria or other large organisms are demonstrable. Clinically there is evidence of meningeal irritation, but encephalitis and/or myelitis may also be present. The cells in the cerebrospinal fluid are usually predominantly mononuclear, but in some instances, notably in the presence of acute anterior poliomyelitis, the polymorphonuclear leukocytes may exceed the mononuclear cells. The highest cell counts in aseptic meningitides are observed in mumps meningitis, in which there may be over a thousand cells, 90 to 95 per cent of them mononuclear. Other viral diseases of this group include western and eastern equine encephalitis, St. Louis encephalitis, Japanese B encephalitis, measles meningoencephalitis, chickenpox meningoencephalitis, lymphocytic choriomeningitis. There are other conditions in the aseptic meningitides category, such as infectious mononucleosis, which are probably of viral origin. Confirmation of the diagnosis by culture of the virus in chick embryos or laboratory animals or by demonstration of a rise in specific antibody titer during the course of the disease may be possible in some instances.

Therapy in this group is largely symptomatic, although aureomycin has been tried (inconclusively) in the treatment of mumps meningitis.

It is important to note that purulent meningitides which have been reduced in severity by partial treatment may be mistaken for aseptic meningitides. Since therapy is dictated by exact diagnosis, careful differentiation is essential. All the suggested diagnostic aids previously referred to must be kept in mind in trying to determine the infectious agent. Perhaps the chick embryo culture is the most valuable of all in coaxing the infecting cocci or bacilli to grow luxuriantly enough to be identified.

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Cerebral Thrombosis and Embolism

A Method of Treatment

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SUMMARY

Acute cerebral thrombosis and embolism give rise to arterial spasm, edema, and anoxia of the cerebral tissues supplied by the affected artery or arteries. Sympathetic block induced by injecting the stellate ganglion with procaine appears to relieve spasm and results in improved cerebral circulation and clinical improvement in a significant number of cases. Sympathetic block should be combined with the usual supportive measures and not infrequently with anticoagulants. Every effort should be made to institute treatment as soon as possible after the onset of symptoms.

IN recent years there has developed a more dynamic approach to the treatment of acute cerebral thrombosis and embolism, due in large part to the increased interest and success in the treatment of peripheral vascular disease through the use of antispasmodic drugs, sympathetic block, and anticoagulants. While various investigators are in sharp disagreement as to the vasomotor reaction of the cerebral blood vessels even with sympathetic block, clinicians have generally accepted the occurrence of fleeting and reversible vascular phenomena as explanation of, for example, the manifestations of migraine and the rapid recovery from an apparently severe cerebrovascular lesion and from brain trauma.

It is the author's conception that intense vascular spasm, edema, and anoxia may result from an acute thrombotic lesion or embolism, which may be responsible for the majority of symptoms manifested by the patient. This concept is supported by the clinical work of Gilbert and de Takats[4] and by the experiments of Villaret and Cachera.[5] The latter investigators produced artificial cerebral embolism in dogs and watched the pial vessels through windows in the skull. Photographs demonstrated the occurrence of spasm of the pial vessels even in areas not directly affected by the embolus which at times persisted for weeks. The author therefore proposes a method of treatment of acute cerebral thrombosis or embolism which emphasizes the use of stellate block combined with the ordinary supportive measures and occasionally anticoagulants. This is largely based on work done on the neurologic service of the Los Angeles County General Hospital,[1] in which it was found that cerebral thrombosis and embolism responded equally well to this method of treatment. Similar results have been described previously by various investigators.[1,2,4]

Diagnosis is the point of beginning for determining the treatment to be used for any patient who has a cerebral vascular lesion. The criteria for the diagnosis of cerebral thrombosis, cerebral embolism, and cerebral hemorrhage are as follows:

Cerebral Thrombosis. It should be reiterated that the clinical manifestations in this condition are not solely the result of sudden occlusion of an artery but rather are due to a combination of vascular spasm and anoxia of the tissues involved, which may ultimately produce an area of softening without definite arterial occlusion.[3]

The patient is usually in advanced years, may or may not have cardiovascular renal disease, and often there is history of previous coronary thrombosis. Thrombosis may frequently develop in patients with a debilitating illness and occasionally will occur apparently simultaneously with acute coronary thrombosis. The onset of symptoms is gradual; thrombosis usually develops during the rest, and ordinarily is not accompanied by unconsciousness, although confusion and stupor may appear. Occasionally there may be a series of premonitory symptoms such as numbness, weakness, or even language disturbance, which subside after a few hours only to recur, until finally they become permanent. Spinal fluid examination is essential. Usually no increase in pressure is observed, although there are a few exceptions, and the fluid is clear, with no significant change in cell count or total protein.

Cerebral Embolism. This diagnosis is made when a patient with a sudden cerebral insult has a cardiac or vascular lesion which can be a source for the embolus or has embolic phenomena elsewhere in the body. Typically, there is unconsciousness, with clinical evidence of a severe intracerebral lesion. The spinal fluid is clear, under no increase in pressure, and shows no change in cell count or total protein content.

Cerebral Hemorrhage. This condition usually appears in persons who have hypertension but who have not had much cardiac damage therefrom. They are younger than those in whom cerebral thrombosis occurs. Symptoms usually develop during stress. They are abrupt in onset and coma usually develops rapidly. At this point the blood pressure

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may have fallen, so that it is within normal limits. Accurate diagnosis, again, depends on the history of onset, the clinical findings, and spinal fluid examination which frequently shows increased pressure (over 160 mm. of water) and, in the majority of cases, blood-tinged fluid.

Once the diagnosis of cerebral thrombosis or embolism has been established, treatment should be started promptly. In the author's experience, stellate block produced on the side of the lesion within six hours after the onset of symptoms gives the most satisfactory results. Often within a few minutes after the injection is completed the patient notices and demonstrates increased motor function in the affected limb or limbs. If he has any speech disturbance it may be improved, and often he appears more alert mentally. Of ten patients treated at the Los Angeles County General Hospital within the first six hours after the development of symptoms, nine showed definite improvement.[1] This procedure should be repeated daily for about four days if the improvement noted after the first block is not sustained.

The stellate ganglion lies near the junction of the body and the transverse process of the seventh cervical vertebra. The sympathetic nerve supply to the cerebral vessels is carried upward to the carotid plexus by way of the stellate ganglion. Therefore, blocking of this ganglion with procaine will deprive the cerebral vessels of their sympathetic nerve control and result in vasodilatation. Block may be successfully and safely produced by the anterior approach.

At a point about 2 inches superior to the sternal notch, just lateral to the trachea and medial to the great vessels and the inner border of the sternocleidomastoid muscle, a dermal wheal is made with 1 per cent aqueous procaine, and a 22-gauge needle, without stilette, is inserted close to the edge of the trachea. The great vessels of the neck are retracted with the other hand. The needle is directed posteriorly, perpendicular to the vertical axis of the vertebral column. The area to be infiltrated is near the lateral aspect of the seventh cervical vertebra. After bone is reached aspiration is performed to determine whether any blood vessels, the lung, or the spinal canal have been punctured. Ten cc. of 2 per cent procaine is then injected and, if the procedure is successful, Horner's syndrome will appear within 20 minutes. If Horner's syndrome does not develop, the injection should be repeated.

In addition to stellate block, general supportive measures should be instituted as indicated. To insure as adequate cerebral circulation as possible, patients should be given oxygen if there is any respiratory embarrassment or cyanosis. Mucus should be aspirated and the foot of the bed elevated, especially for the patient with thrombosis. Adequate fluid intake (3,000 to 4,000 cc. daily) should be maintained, using the intravenous method if the patient is unable to take fluids orally. Nicotinic acid in doses of 50 to 100 mg. three times daily is given for its vasodilating effect. The author has had no experience with benzazoline hydrochloride.

If the patient remains unconscious more than 48 hours, nutrition should be supplied by tube feedings. Sedation should be used sparingly—in amounts sufficient to produce the desired effect without deep narcosis. Pentobarbital in doses of 0.1 to 0.2 gm. is usually adequate. If the patient is unable to take medication orally, pentobarbital may be given rectally or sodium phenobarbital may be administered hypodermically. Urinary incontinence or retention should be treated according to present-day urologic principles.

Anticoagulants may be used in conjunction with stellate block, or alone in certain instances in which block appears to be ineffective or not indicated. Gilbert and de Takats[4] recommended the use of anticoagulants in conjunction with stellate block in cerebral embolism. When there is progression of symptoms in spite of stellate block and supportive measures, especially if the lesion is on the major side and causing some disturbance of language, use of anticoagulants is imperative. In an occasional case there occur episodes indicating some cerebral circulatory disturbance from which the patient recovers in a few hours only to have recurrence in a few days. This cycle is repeated at intervals until recovery is incomplete. In such circumstances, the author has obtained excellent results from the use of Dicumarol.®

Intravenous administration of procaine, using 0.5 gm. to 1.0 gm. in 500 cc. of saline solution, can be utilized if stellate block is not available. While it does seem to be beneficial in some cases, the results are not comparable with those obtained with stellate block.

Treatment as outlined in this presentation, especially as regards the use of anticoagulants, should be followed only in cases in which the diagnosis of cerebral thrombosis or embolism is certain. If cerebral hemorrhage cannot be definitely ruled out, general measures only should be used. While the best results appear to be obtained when treatment is instituted early, not infrequently improvement is obtained in cases in which the lesion is several days old. This is especially true if the patient is young.

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The Conservative Treatment of Myasthenia Gravis

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SUMMARY

Neostigmine is at present the mainstay in treatment of myasthenia gravis. Adjuvant therapy with ephedrine, potassium chloride, or guanidine is recommended. Urecholine,® also used as an adjuvant, is still in the experimental stage and should only be given by one acquainted with its properties and toxic effects. Di-isopropylfluorophosphate and tetraethyl pyrophosphate likewise are still in the experimental stage. Since they are extremely toxic and unstable, general use of them is discouraged until further experimental and therapeutic studies are completed. The results of thymectomy and radiation of the thymus are equivocal and these procedures should be reserved for severe cases which should be selected only after a thorough study.

THE modern treatment of myasthenia gravis is based on knowledge of the synaptic transmission of motor impulses at the myoneural junction by acetylcholine. Since Walker's discovery that physostigmine and neostigmine improved the symptoms of myasthenia, it has been assumed that this disease might be explained in terms of curarizing effect.[22,23] Curare and quinine exaggerate the symptoms of myasthenia gravis.[1,10] On the other hand, drugs which inhibit the enzyme cholinesterase and which therefore serve to protect acetylcholine are beneficial in myasthenia gravis. These facts have lent credence to the theory of curarizing effect. The precise reason for the failure of synaptic transmission, however, remains obscure.

More recent evidence has suggested that myasthenia is caused by a deficiency of acetylcholine, that is, by "cholinergic insufficiency."[3,12] Treatment today is based on the concept that the disease is caused either by curarizing effect or by cholinergic insufficiency, with the additional postulation that one or the other of these theoretical causes might stem from thymic or endocrine disturbances.

The drugs which act as cholinesterase inhibitors (decurarizing effect) are prostigmine bromide, neostigmine (prostigmine methylsulfate), potassium chloride, ephedrine sulfate, and guanidine.[7,14,19,20]

Neostigmine is the most effective drug in the therapy of myasthenia gravis and, because it is also relatively non-toxic and safe, is the drug of choice. The dosage may vary from 15 to 30 mg. (one or two tablets) two or three times daily, in mild cases, to as high as 30 mg. six times daily in more severe cases.[21] If the patient has difficulty starting oral medication in the morning or tends to choke with eating, a combination of oral and parenteral administration may prove of value. In this case, the usual oral dose should be supplemented with 0.5 to 1.0 mg. of neostigmine given intramuscularly in the morning and one hour before meals.[20] In severe cases, intramuscular administration may have to be relied upon. The dosage may vary from 0.5 to 2.5 mg. of neostigmine as required. Parenteral doses as high as 1.5 mg. hourly have been reported.[20] The emergency treatment of myasthenia in severe exacerbations consists of 1 to 2 mg. neostigmine given intravenously. The intelligent patient, under supervision of a physician, will soon learn to vary the dosage, both oral and parenteral, according to the severity of symptoms. The undesirable gastrointestinal side-effects of neostigmine are adequately controlled by atropine sulfate. In mild cases tincture of belladonna gives good results.[9] In more severe cases, where parenteral administration of neostigmine is required, atropine sulfate (0.6 mg.) should accompany the neostigmine injection.

As neostigmine is an agent of transient action, adjuvants are required to prolong its effect. Ephedrine, potassium, and guanidine are useful in this connection. Ephedrine sulfate, in doses of from 8.0 to 24.0 mg. two or three times daily, is recommended.[8] Potassium chloride must be given in doses of from 4 to 6 gm. six times a day.[14] The gastrointestinal and urinary side-effects of potassium therapy may be reduced if it is taken in specially prepared eggnogs, orange juice, or tomato juice.[19] The results of guanidine therapy have been equivocal. The usual recommended dose is from 10 to 25 mg. per kilogram of body weight, but in severe cases from 20 to 50 mg. per kilogram of body weight daily, administered in three divided doses, may be necessary.[7,15]

In addition to such drugs, certain general therapeutic measures should be emphasized. The avoidance of fatigue must be stressed, and reassurance is constantly necessary. Physiotherapy, narcotics, anesthetics, quinine, curare, and desiccated thyroid should be avoided since they may exaggerate the myasthenic condition. During exacerbations careful nursing attention is necessary.

Two new agents, di-isopropylfluorophosphate and tetraethyl pyrophosphate, are being used experimentally.[6,18] Presumably the potent toxic effect of fluorine on enzyme systems inactivates cholinesterase.[6] Preliminary clinical reports of di-isopropylfluorophosphate and tetraethyl pyrophosphate indicate good clinical results. Tetraethyl pyrophosphate is the least toxic, but the margin between the effective

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dose and the dangerous dose is narrow; and it is not as potent an inhibitor of cholinesterase as is neostigmine. More prolonged action is its chief attribute. Convulsions and gastrointestinal symptoms are the most frequent symptoms of intoxication from use of these two drugs. Both are extremely unstable in the presence of water, and dosage is difficult to maintain.[16] Consequently, di-isopropyl-fluorophosphate and tetraethyl pyrophosphate need further experimental and therapeutic studies before they may be considered reliable and safe.

A few words with respect to cholinergic-stimulating therapy in myasthenia therapy may be in order. Urecholine®* (B methylcholine urethane), which has a parasympathetic-like action, was suggested to the authors as an adjuvant in myasthenia gravis. This drug is stable and has a prolonged action in producing nicotine-like effects.[17] It is less toxic than other choline derivatives. Electromyographic studies following subcutaneous injection of Urecholine (0.5 mg.) in patients with myasthenia showed an increase in muscle action potentials similar to those observed after neostigmine. Although the observed response was weaker than the response obtained with neostigmine, it was more prolonged, which suggests that Urecholine may be a useful adjuvant to neostigmine therapy in myasthenia gravis. Clinical studies of the drug which are being made by the authors are still in an initial phase, however, and results thus far do not permit an evaluation of the usefulness of this agent in myasthenia gravis.

A review of the therapy of myasthenia gravis would not be complete without some mention of the recent studies on the thymus gland. Treatment of the thymus has involved two approaches, radiation and operation. The presence of a thymic tumor, as demonstrated by x-ray in patients with myasthenia gravis, by no means justifies thymectomy. The results of thymectomy have been variable, and since spontaneous remission occurs in approximately 25 per cent of myasthenic patients, the results of thymectomy are difficult to evaluate.[11] In addition, it must be remembered that the estimated mortality of thymectomy is from 20 to 25 per cent and that only some 25 or 30 per cent of myasthenic patients are suitable subjects for the operation. Thus, thymectomy is not only hazardous,[13] but its effects are equivocal. The recent reports of Clagget and Eaton,[5] Blalock,[2] Keynes,[13] Harvey,[11] and Castleman and Norris[4] lead to the conclusion that final evaluation of thymectomy in myasthenia gravis will require further study. The results of radiation therapy on the thymus gland have also been equivocal.

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Spontaneous Subarachnoid Hemorrhage

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SUMMARY

Sudden development of pain in the head followed by evidences of meningeal irritation, with or without motor or sensory symptoms or signs, is almost pathognomonic of subarachnoid hemorrhage. The final diagnosis rests upon the demonstration of blood in the cerebrospinal fluid. If the hemorrhage is massive, or from an aneurysm of an unprotected arterial trunk, the patient may die in a comparatively short time. If the bleeding is less abundant and from an aneurysm which is protected by adjacent structures the patient may survive. Angiography should probably be done early in most cases. If neurological signs or the results of angiography indicate that the aneurysm is in such a location that surgical treatment is feasible it should probably be undertaken. If medical treatment is to be carried out the patient should have protracted rest, frequent spinal drainage so long as the cerebrospinal fluid contains blood or is under materially increased pressure, sedatives and analgesics, and passive movements of the neck and limbs to forestall limitation of motion of joints.

SPONTANEOUS subarachnoid hemorrhage is a non-traumatic extravasation of blood into the subarachnoid space, the area between the pia mater and the arachnoid which is normally filled with cerebrospinal fluid. For more than a quarter of a century it has been recognized that in most cases hemorrhage of this sort is due to rupture of an aneurysm of the circle of Willis. In addition, certain systemic infections and dyscrasias of the blood, as well as arteriosclerosis, rare vascular anomalies and hemangiomatous tumors of the brain may result in bleeding into the subarachnoid space.

CAUSATIVE FACTORS

Aneurysms of the arteries of the brain are more common than those in other vessels. True aneurysms, however, are not often seen in the brain itself but tend to involve the arteries of the base before they or their branches enter the brain. The internal carotid artery and its terminal anterior cerebral and middle cerebral arteries are particularly likely to show aneurysmal dilatation.

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The most important factors in the causation of cerebral aneurysms are, in order of ascending importance, infection, arteriosclerosis, and inherent weakness of the walls of the arteries which form the circle of Willis or of the larger branches of those arteries. In turn, intracranial aneurysms may be divided logically into three groups, the mycotic or embolic, the arteriosclerotic or fusiform and the saccular or "berry" type. In Dandy's[3] series of 108 cases 4.5 per cent were of mycotic nature. In such cases there is usually a history of antecedent subacute bacterial endocarditis, pyemia, or purulent disease of the lungs. Rupture of an aneurysm of this type is usually a terminal development. The arteriosclerotic or fusiform aneurysms tend to involve the larger arterial trunks, particularly the basilar and vertebral arteries. In Dandy's series, 22 of the cases (16.2 per cent) were of that classification. In most of the cases in that group the diagnosis was made at operation or necropsy. The saccular or "berry" type of aneurysm is commonly agreed to be due to congenital defects. It was first described by Virchow, was called "miliary" aneurysm by Charcot, and "berry" aneurysm by Richardson and Hyland.[7]

EMBRYOLOGY

Forbus[4] described a muscular defect of the media at points of bifurcation, not only in the arteries of the brain, with and without aneurysmal formation, but in arteries elsewhere in the body. The defect was so commonly encountered as to indicate that it is relatively normal. It was possible to show that these muscular defects began in embryonic life. From study of the time and mode of development of the muscular coat of arteries, Forbus arrived at a theoretic explanation of the failure of muscular development at points of bifurcation. The muscular coat of any vessel develops at an earlier period than that of its branches, from a group of mesenchymal cells, separate and distinct from those forming the muscularis of the branches. A failure of the two separately developing muscular coats to fuse properly offers a possible explanation of the later observed defects. Forbus concluded that miliary aneurysms of the superficial cerebral arteries and most probably those of all arteries of medium size, occur quite independently of any inflammatory process, arteriosclerosis or external trauma, and that these aneurysms as such are not congenital malformations but are acquired lesions arising from a combination of focal weakness (the result of a congenital defect of the muscularis) with degeneration of the internal elastic membrane due to continued over-stretching of this structure.

Dandy[3] and a co-worker (Dorcas Hager) concluded from a study of the material of the Carnegie Embryological Collection that the adult pattern of

the circle of Willis may be recognized as early as the second embryonic month, and that the early process of development of this structure is characterized not by the outgrowth of definitive vessels as such but by the elaboration of certain channels and the total disappearance of others in "an all embracing primitive plexus." From their work it would appear that as arterial trunks are developed from this primitive capillary network, numerous vessels are absorbed. The sites of absorption of these vessels are believed to represent weak points from which miliary or "berry" aneurysms arise. This hypothesis would explain the development of an aneurysmal sac with a narrow neck as the result of the incomplete disappearance of one of these vessels. The residual tiny protrusions which are present at birth apparently slowly increase in size with age. It is noteworthy that many of the aneurysms of the internal carotid artery within the cranial chamber arise where there are no branches and at points where primitive vessels were absorbed. The aneurysms of the anterior communicating artery frequently arise from the site of origin of the primitive median anterior cerebral artery. Syphilis plays little, if any, part in the formation of these aneurysms.

AUTOPSY DATA

In the course of a review of the results of 30,000 autopsies, Courville[2] encountered 96 aneurysms of the circle of Willis. Eighty-three of them were of the saccular or berry type. Thirty involved the anterior cerebral and anterior communicating arteries, 22 were at the point of bifurcation of the internal carotid into the anterior and middle cerebral arteries, 26 at bifurcations of the middle cerebral arteries, one at the junction of the posterior cerebral and posterior communicating arteries, and four at the bifurcation of the basilar artery to form the posterior cerebral arteries.

In size saccular aneurysms vary from a few millimeters to as much as 5 cm. in diameter. The walls may be the thickness of the parent vessel or may be as thin as tissue paper. Multiple aneurysms are not uncommon. Dandy reported one patient with five aneurysms. In general they are somewhat more common in females than in males. Symptoms have been noted in patients younger than two years of age[3] and older than 70.

SYMPTOMS

In some instances there are prodromal symptoms. Sudden repeated sharp pains in the eyes or in the frontal or temporal region followed by ptosis of an upper eyelid and extraocular palsies are almost pathognomonic of carotid aneurysms. A suspicion of rupture of a congenital aneurysm of the circle of Willis should arise whenever sudden symptoms of intracranial origin develop. The diagnosis is established if the cerebrospinal fluid is bloody or yellow.

An aneurysm of an artery of the brain, however, may give rise to no symptoms until the moment of rupture. At that time the patient may speak of "something snapping in the head."[1] This is associated with or followed by pain of great severity which may radiate to the frontal region, or may be referred to the occipitonuchal region. Subarachnoid hemorrhage is usually slow, but may be rapid in onset and may lead to violent symptoms such as falling, loss of consciousness, deep coma, generalized convulsions, cranial nerve palsies, partial or complete paralysis, slowing of the pulse rate, elevation of temperature and death. If the initial hemorrhage is massive or from an unprotected arterial trunk, death may result within a matter of hours. In other cases bleeding may recur at intervals for hours or days in smaller amounts.

Anteriorly placed aneurysms may compress the optic nerve with unilateral diminution in the acuity of vision. Sometimes an optic tract is compressed, resulting in a hemianopic defect. An aneurysm of the middle cerebral artery may lead to monoplegia or hemiplegia. Aneurysms of the posterior communicating artery are particularly likely to be associated with oculomotor or third nerve palsy and possibly hemianopia due to compression of the corresponding optic tract. Aneurysms of the basilar artery may result in paralysis on both sides or be characterized by alternating hemiplegia.

If daily lumbar puncture is practiced it will be observed that the supernatant fluid, which at first is usually deep red, becomes yellow in three or four days. Erythrocytes in appreciable number give a cloudy appearance to the cerebrospinal fluid. The cloudiness diminishes as the blood is hemolyzed, provided no further bleeding occurs. For several weeks after the initial hemorrhage, erythrocytes in diminishing number may continue to be present in the cerebrospinal fluid. As a result of the irritation of the leptomeninges by the blood, residual pleocytosis which is chiefly of mononuclear type frequently develops. There may be a few polymorphonuclear cells. So long as blood is present, and sometimes for rather long periods afterward, the cerebrospinal fluid is liable to be under materially increased pressure. Pressures as high as 300 to 400 mm. of water are frequently encountered. The total protein content of the fluid is elevated. In one case observed by the author, 180 mg. per 100 cc. was recorded, but as a rule the total protein content does not exceed 100 mg. per 100 cc.

Hemiplegia or hemiparesis is a relatively common finding and is most commonly encountered in aneurysms involving the middle cerebral artery. Persistent loss of motor function may be due to associated cerebral thrombosis or to local pressure from an aneurysm. Transient symptoms of paralytic nature may be due to cerebral edema or to the formation of a hematoma. The presence of monoplegia restricted to a lower limb is presumptive evidence of involvement of an anterior cerebral artery. Loss of power on both sides usually may be taken as evidence of basilar or vertebral arterial involvement. Babinski's sign is of value when it is unilateral. When it is bilateral it is probably due to the irritating effect of blood over the convexity of the cerebrum.

Convulsive seizures occurred in 20 per cent of Dandy's cases.[3] Focal seizures are more common where there is involvement of the anterior or middle cerebral arteries. Papilledema is occasionally encountered. Subhyaloid hemorrhage following episodes of abrupt loss of consciousness is often of great diagnostic significance. It is due to extension of the hemorrhage along the subarachnoid sheaths of the optic nerves.

ROENTGENOGRAPHY

Occasionally evidence obtained by roentgenographic examination of the skull is of great diagnostic value,[6,9] particularly where aneurysms involve the vessels of the anterior part of the circle of Willis. Recognition of an aneurysm on this basis rests upon the discovery of evidence of calcification in the walls of the aneurysm or erosion of bone adjacent to the aneurysmal sac. In the first instance there are plaques of calcium beside the sella turcica which are generally semilunar in shape with the convexity upward. These appear as fine, curvilinear shadows, sharply outlined, occasionally segmented and easily recognizable as lying in the wall of a cystic or rounded structure. As a rule, however, the diagnosis and localization of an aneurysm is possible only in cases in which there is intermittent leakage and focal signs, or in instances in which aneurysms have been demonstrated by angiographic studies.

ANGIOGRAPHY

The introduction of angiography by Moniz in 1927 opened new avenues of diagnostic thought. In 1933 Moniz[3] localized an aneurysm by this method. Since that time angiography has been employed to an increasing degree as an aid to diagnosis where variations from the normal cerebrovascular pattern have been considered reasonable possibilities. While carotid angiography is generally the method of choice, vertebral angiography must sometimes be performed if evidence of involvement of the posterior communicating or the posterior cerebral arteries is to be demonstrated. Dandy was of the opinion that this procedure was generally unnecessary since it was usually possible to postulate with reasonable accuracy the side on which the lesion is located. Since most aneurysms involve the carotid trunks or their terminal anterior and middle cerebral arteries, he felt surgical exploration justifiable without the added risk of angiography.

Ventriculography is of no diagnostic value except in those instances in which the aneurysm is very large and is producing symptoms by pressure on adjacent structures.[3]

TREATMENT

The problem of treatment has received a great deal of consideration. Symonds[12] recommended daily spinal puncture. Others have looked with disfavor on this procedure. It is the author's opinion that so long as the cerebrospinal fluid contains blood and the pressure is significantly elevated, frequent spinal drainage should be carried out. In several instances in which bradycardia was present the pulse rate became normal after reduction of the pressure from 350 or 450 mm. of water to 100 mm. or less. Absolute rest in bed for a long period is mandatory. It has been the author's practice to limit the intake of fluids rather sharply, to put the patient on an acid-ash diet in order to facilitate elimination of calcium, to give small amounts of phenobarbital several times daily as a sedative and to relieve pain by morphine or other appropriate analgesic medication. Very often the inhalation of oxygen will relieve a headache and partially clear the sensorium. It is imperative that the patient be able to have a bowel movement daily without the necessity of straining. Mild catharsis or enemas are generally effective. In one case large doses of fluid extract of cascara were required. Passive movement of the neck and limbs should be carried out to forestall limitation of motion of joints.

NEUROSURGICAL TREATMENT

There is considerable divergence of opinion as to the indications for neurosurgical treatment. Richardson and Hyland[7] recommended that surgical efforts be restricted to larger aneurysms causing focal symptoms. Dandy,[3] on the other hand, was of the opinion that surgical intervention was highly desirable in view of the high mortality rate associated with the first subarachnoid hemorrhage and of the frequent recurrences. For lesions in the cranial chamber or in the cavernous sinus he recommended occlusion of the internal carotid, provided Matas' tests of partial and later complete occlusion of the ipsilateral internal carotid artery did not lead to serious symptoms of cerebral anemia. Hamby expressed preference for contralateral common carotid occlusion as a test for the efficiency of the collateral circulation of the circle of Willis. If both of these tests give satisfactory results, the common or the internal carotid artery may be occluded by fascial strips, plication or tantalum clips. Hamby believed that it is safer to occlude the artery of choice partially for seven to ten days and then to make the occlusion complete. If an aneurysm has a neck, it may be clipped intracranially. The mortality rate for intracranial operation on aneurysms of the circle of Willis, however, is 25 per cent. Surgical treatment of aneurysms of the middle cerebral and anterior communicating arteries is extremely hazardous. In three cases upon which Hamby operated, bilateral closure of the anterior cerebral arteries was necessary. Of these patients, two died and the third became "paralytic and practically amental."

With conservative treatment healing is brought about by the formation of a clot in the region of the aperture in the vessel. At times the thrombosis may be propagated to such an extent that occlusion of the parent vessel occurs resulting in symptoms referable to the anterior, middle or posterior cerebral arteries. In one case observed by the author, this

process resulted in the development of right hemiparesis and of a considerable degree of aphasia in a patient in whom paralysis of the left oculomotor nerve was manifest at the time of onset of symptoms.

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Evaluation of Therapy of Peripheral Polyneuritis

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SUMMARY

Peripheral polyneuritis is not a disease entity but a mystery. The underlying cause should be searched for, but since often it cannot be found, treatment should be started simultaneously with the search. Conservative measures should be tried first—vitamin B complex, niacin, riboflavin, pyridoxine and thiamine chloride; next, injections of liver extract. Then, if no specific condition amenable to treatment has been discovered and if the patient is seriously incapacitated and becoming worse, hospitalization for trial with BAL is indicated.

PERIPHERAL polyneuritis is not a disease entity but a syndrome in which the longest neurons in the body are bilaterally, symmetrically affected. It may be due to countless conditions. The effect may be motor, with weakness of the hands and legs, or sensory with glove-and-stocking impairment. Most often it is mixed, both motor and sensory.

The most interesting advance in therapy is the treatment with BAL (2, 3-dimercaptopropanol). This has been found successful not only in cases due to arsenic poisoning, but also in those due to infection or vitamin deficiency.

BAL was developed experimentally as an antidote to arsenic poisoning. The mechanism is as follows: Certain enzymes, including the pyruvate oxidase system, function through their sulfhydryl groups. In arsenic poisoning the arsenic combines with these sulfhydryl groups, making the enzyme inactive. Inactive enzymes disrupt metabolism, and the patient gets sick. BAL has sulfhydryl groups which possess a greater affinity for arsenic than do the sulfhydryl groups contained in enzymes. Therefore, in the presence of BAL, arsenic becomes dissociated from the enzymes to unite with the BAL. The enzymes are liberated. There is renewal of enzyme activity and resumption of metabolic function. The patient improves. The compound formed by the BAL-arsenic combination, BALthioarsenite, is chemically stable, harmless and rapidly excreted by the patient.

BAL is efficacious in the treatment of intoxication with certain heavy metals—arsenic, mercury, gold and antimony. But it is contraindicated for lead neuritis and in cadmium disease. The BAL-lead and BAL-cadmium compounds are more toxic than either lead or cadmium alone.

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BAL is useful in heavy metal poisoning because it reactivates the enzyme equilibrium. On the theory that peripheral polyneuritis resulting from causes other than heavy metal intoxication also may be due to disruption of enzyme equilibrium, Nielsen[2] recommended trial of BAL in cases of peripheral polyneuritis which did not respond to other measures. Treatment with BAL was given at Birmingham Hospital in 1948 by Furmanski,[1] at the Los Angeles County General Hospital, and by Nielsen in private practice. In several instances results were striking. Patients whose condition was getting worse despite administration of large doses of liver extract and vitamins began to improve within a few days of the administration of BAL, and later became ambulatory. In these cases the peripheral polyneuritis was associated with virus infection, and with non-specific anemia and with alcoholism and/or avitaminosis. In all instances symptoms were of recent onset. Therapy is of benefit only when the metabolic disturbance is reversible. With continued disease of the nervous system there is progressive demyelinization of the nerves. Eventually no treatment cures.

A syndrome which may be confused with peripheral polyneuritis and which also in the early stages may be amenable to BAL therapy is infectious neuronitis, or the Guillain-Barré syndrome. The patient may have signs of peripheral neuritis; signs of transverse myelitis, with Babinski reaction or inability to void urine; and signs simulating those of anterior poliomyelitis, along with facial or other cranial nerve paralysis. Diagnosis is simplified if suspicion of neuronitis is aroused by acute onset suggestive of virus infection, and by an increase in protein but a low cell count in the spinal fluid. If the patient does not die of the disease—the death rate is about 20 per cent—prognosis for return of function is good. In some cases BAL has proved amazingly effective, in others ineffective.

BAL is available in 10 per cent solution in 20 per cent benzylbenzoate in peanut oil. It should be injected deep into the muscle. Dosage varies with the condition and with the patient. In peripheral polyneuritis 2.5 mg. per kilogram of body weight should be given every six hours. The length of treatment depends on the response of the patient. Occasionally treatment has to be discontinued because of extreme soreness of the gluteal muscles, cold abscesses, vomiting or untoward consequences such as bulbar paralysis. BAL is a potentially hazardous drug. Use of it is indicated in cases of heavy metal poisoning and possibly in fulminating infectious disease of the nervous system. In other cases it should not be used unless conservative measures have proved futile.

Conservative measures include the use of vita-

min B. This certainly should be tried first, particularly in cases in which there is history of vitamin deficiency or in which associated physical findings are suggestive of it. According to Strauss,[3] Wintrobe produced peripheral polyneuritis experimentally with diets adequate in thiamine chloride but deficient in the other vitamin B components. Therefore in the treatment of peripheral polyneuritis all the vitamin B complex should be given—crude vitamin B supplemented by riboflavin, pyridoxine and nicotinic acid as well as thiamine chloride.

Injections of liver extract often have proved helpful even when there was no demonstrable anemia. Patients should receive therapeutic trial with both crude and pure liver extract in massive doses.

The general care of the patient is important: The feet should be splinted to avoid foot drop. During the early irritative stage a cradle should be placed over the limbs to protect them from the irritation of bedclothes, which may cause intolerable pain. Gentle heat may afford relief. Decubitus ulcers should be prevented by judicious padding and frequent changes of position. The patient should be kept clean, dry, comfortable and happy—quite an undertaking if the disease is extensive, with paralysis of the arms as well as of the legs. After the irritative stage is over, light massage and gentle exercise of the affected parts may be instituted and then cautiously increased. Anything that is painful to the patient is contraindicated. Increase of pain is a sign that either the patient or the physiotherapist is doing too much, and that the activity must be reduced or temporarily discontinued. When the patient at last becomes ambulatory he should wear arch supports, since the small muscles of the foot are the last to regain function.

Physical therapy is exceedingly valuable and should be administered by a trained physical therapist. It hastens rehabilitation after an acute episode, and it is the only measure which may help the patient with long-standing peripheral polyneuritis.

Peripheral polyneuritis may be the first manifestation of any of a number of diseases. Therefore, if the cause is not apparent, the temptation to diagnose avitaminosis should be resisted. Instead, careful search for a cause should be made. The possibility of pernicious anemia should be investigated. Blood examination, gastric analysis and therapeutic trial with liver extract should be carried out in cases in which the cause is obscure. In patients with known pernicious anemia the number of erythrocytes per cu. mm. should be kept over six million if possible in order to prevent central nervous system complications.

Next, diabetes must be considered. Central nervous system disease tends to occur in association with low grade diabetes that is fairly well controlled without insulin. The onset of peripheral polyneuritis may be the first sign of the disease; in a patient known to have diabetes, it may be the signal for more strenuous treatment of that condition.

Hematoporphyrinuria is another condition often associated with peripheral polyneuritis. A 24-hour specimen of urine should be examined for porphyrin bodies. The presence of porphyrin signifies a metabolic disturbance. When this is due to liver dysfunction the patient may be helped by nicotinic acid in doses of at least 50 mg. per day.

Other conditions causing peripheral polyneuritis include hypoglycemia, hyperthyroidism, chronic gastrointestinal or liver disease, acute and chronic febrile illness, diphtheria, leprosy, Boeck's sarcoid disease, parasite infestation, periarteritis nodosa, peripheral vascular disease and malignant neoplasms. These all should be at least considered.

Finally, the possibility of chronic or acute poisoning must be investigated. Considerations in this regard are the medication the patient is taking, arsenic poisoning from the careless use of ant powder or the consumption of unwashed previously sprayed fruit and vegetables, carbon monoxide poisoning, triorthocresyl phosphate contamination of liquor (as a cause of so-called "jake" paralysis) or possibly of cooking oils. (The contamination of cooking oils has been reported in other countries but to date not in the United States.) Also to be considered is absorption of noxious chemicals by inhalation or percutaneous route from insect sprays, dyes, cleaning fluids and similar volatile compounds at home or at work.

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The Contribution of Cerebral Angiography in Diagnosis

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SUMMARY

Angiography is important in the diagnosis of central nervous system disorders. In operable lesions it not only discloses the location of the lesion but also gives valuable information regarding its character and surrounding vascular architecture.

The technique of both the pericutaneous and the open methods is described. The advantages of the controlled automatic arteriograph are described as well as pertinent information regarding cerebral circulation time.

The choice of contrast media and the advantages and disadvantages of each are described.

The three phases of angiography important in diagnosis—the arterial phase, the capillary phase and the venous phase—are discussed.

The indications and contraindications are briefly outlined with respect to neoplasms, trauma, hemorrhage, aneurysms and other such operable lesions.

The characteristic changes produced by aneurysms, vascular malformations, neoplasms and other space-occupying lesions as related to the circulatory apparatus show variations characterizing the type of lesion encountered.

Angiography in traumatic conditions, while limited, is of exceptional value in the diagnosis of obscure lesions, particularly the subdural hematomas.

THE importance of angiography in the diagnosis of central nervous system disorders cannot be overemphasized. While it does not in any way replace a thorough neurological examination, it does serve as a valuable supplement. Actually, it may be more informative than pneumoencephalography or ventriculography.

By its use, the vascular architecture and often the pathologic character of operable lesions can be determined before surgical intervention. Such information is of the greatest importance in the plans of a successful operation. It is perhaps the only positive method for differentiating between the types of progressive cerebrovascular disease and expanding lesions. Other more obscure lesions, such as aneurysms, arteriovenous complexes, and telangiectases, often cannot otherwise be positively identified.

The gravity of the situation demanding angiography is invariably greater by far than the small risk involved. While the procedure has been slow in gaining popularity, it now ranks with the most important supplementary aids in neurologic diagnosis.

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HISTORY

In 1927 Moniz and Tima established the diagnosis of a temporal lobe tumor in a cadaver by injecting radiopaque material into the carotid artery. They found that a solution of sodium iodide gave good contrast pictures and could be injected so as to visualize cerebral vessels with reasonable safety. Subsequently the procedure became routine in their clinic in suitable cases. The speed of blood flow through the brain was studied. The characteristic difference in the angiographic pattern between meningioma and astrocytoma was established. Changes resulting from trauma, especially subdural hematoma, were reported. Tonnis pointed out the differentiating feature of glioblastoma multiforme and cerebral abscess. Dyes and Fisher elaborated on tumor localization by angiography. Lorenz attempted to classify tumors on the basis of their angiographic pattern (cited by Engset).[6]

Saccular aneurysms were described by Hermann,[10] Dott,[2, 3, 4] and Jefferson.[11, 12, 13] Details of a vascular malformation were reported by Bergstrand, Olivecrona and Tonnis (cited by Engset).[6] In more recent years List,[14, 15, 16, 17] Gross,[8, 9] Poppen,[21] Norlen,[19] Elvidge,[5] Culbreth,[1] Gass,[7] and others have stressed the value of angiography in surgical lesions. These contributions, among others of equal and supplemental importance, have established angiography as another indispensable method of studying diseases of the central nervous system.

TECHNIQUE

As in all roentgenographic studies, good films are essential. Since rapidly moving dye in the cerebral circulations must be photographed, proper equipment and an experienced team are required. Three phases of the circulation are important—the arterial phase, the capillary phase, and the venous phase. The average length of time for blood to travel from the carotid artery in the neck through the brain and back to the jugular vein in the neck is 4.5 seconds. Therefore, a series of films must be exposed during this period of time.

The authors use an automatic film changer which furnishes six exposures in 4.5 seconds.[22] This gives a complete picture of the cerebral circulatory apparatus as well as an evaluation of the circulation

time. Thus alterations of the circulatory mechanism which occur in disease can readily be visualized. Since the blood in the carotid artery moves rapidly, the dye should be injected in a single burst through a 17-gauge needle. Film exposure must be started as the last of the dye leaves the needle. This gives proper timing of films, and 8 cc. of dye when injected rapidly gives adequate concentration in all parts of the vascular system. Anteroposterior and lateral exposures are usually sufficient. Occasionally an oblique view may be desirable and this can be determined by studying the wet films before removing the needle from the artery.

The choice of dye has been the subject of considerable controversy. In this country Thorotrast® and Diodrast® are the most commonly employed. Thorotrast is the least irritating, gives the best pictures, and therefore enjoys the greater popularity. However, it is objected to by a few on the ground that it is radioactive.[18, 20, 23, 24] After injection it is finally deposited in the reticuloendothelial system. In large doses it has been known to cause unfavorable changes in experimental animals. However, experience has shown that the amount required for angiography can be used with safety equal to other media. Diodrast in 35 per cent solution unfortunately is irritating and occasionally causes complications. Further, it gives only fair roentgenographic detail. The authors use both Diodrast and Thorotrast as media. Diodrast is probably preferable for introduction by direct puncture. Further, it should be used if repeated angiographic studies are to be done, in order to avoid an accumulative dose of Thorotrast. In the case of iodine sensitivity Thorotrast should be used in preference to Diodrast.

The introduction of dye into the desired vessel may be accomplished either by the open method or by direct puncture. The open method is commonly indicated for study of aneurysms, certain tumors, arteriovenous fistulae. By this method tolerance to ligation of the vessel can be tested. If compression of the contralateral carotid artery allows the contralateral arterocerebral artery to fill, the anterior communicating artery is adequate and carotid ligation will probably be tolerated.

THE NORMAL ANGIOGRAPHIC PATTERN

Three phases of the circulatory apparatus as previously mentioned must be photographed because study with a single exposure is at best a hit-and-miss proposition. With an automatic film changer permitting six exposures during the circulation time, the three angiographic phases can be readily demonstrated. Usually the first two films demonstrate the arterial system. In the third and fourth films the dye is generally ill-defined since it is broken up in

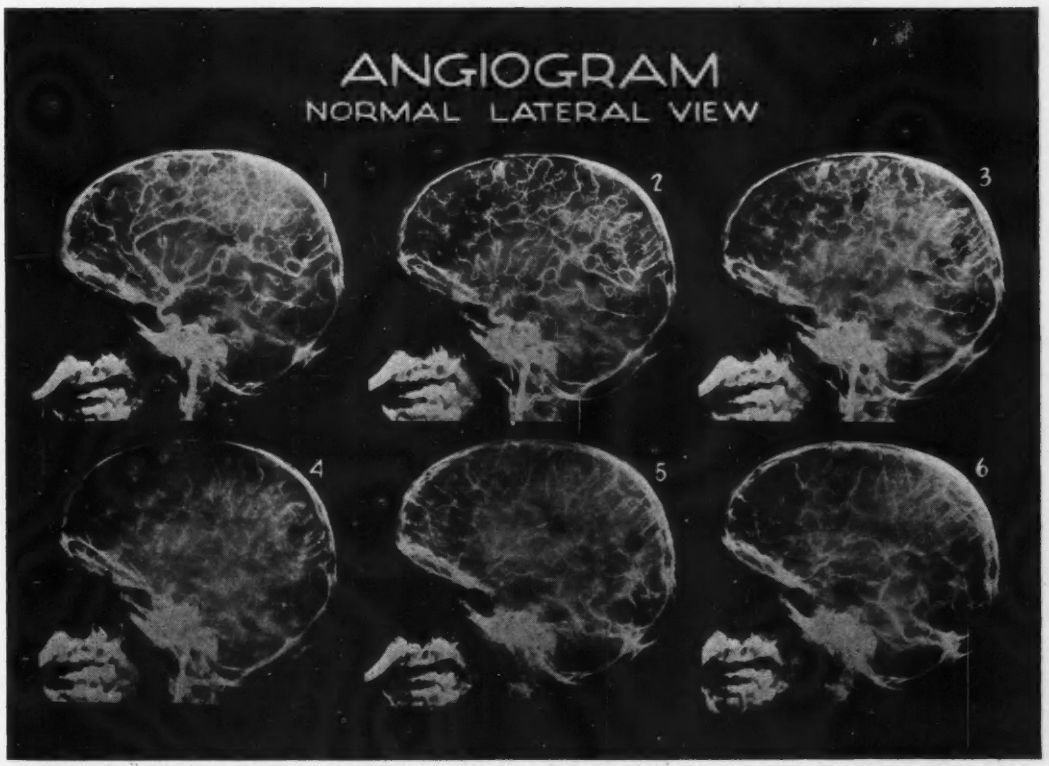

Figure 1.—First films in series show arterial phase. Films 3 and 4 show dye broken up in smaller vessels and capillaries. Film 6 shows large veins and sinuses.

NORMAL CAROTID ANGIOGRAM

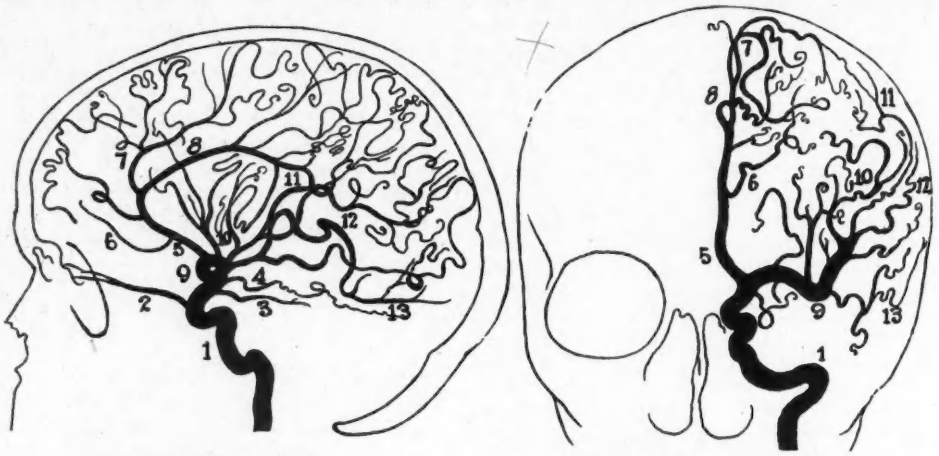

Figure 2.—Drawing made from arteriograms showing principal arteries.

the arterioles, capillaries and venules. In the last two films the dye becomes visible again in the veins and dural sinuses (Figure 1). For practical illustration the blood vessels, which can ordinarily be demonstrated by angiography, have been copied from actual roentgenograms. The cerebral anatomical pattern is shown in Figure 2. The pattern of the veins and sinuses is illustrated in Figure 3. The vertebral pattern is shown in Figure 4.

INDICATIONS

Like other comparable methods of examination, angiography must be employed judiciously. Even though the risk involved is minimal, it can hardly become a routine roentgenographic procedure. On the other hand, most intracranial disorders of an uncertain nature merit its use. Regardless of the type of lesion, if knowledge of the vascular architecture in a particular case is important for surgical repair, angiography is practically mandatory. In the presence of unexplained spontaneous subarachnoid hemorrhage, it is a necessary procedure. It is required for intelligent planning of the surgical management of aneurysms, vascular malformations, arteriovenous fistula, etc. In cases of cerebral lesions with high intracranial pressure, angiography often gives as much information as ventriculography, sometimes more; and it is by far the safer of the two procedures.

The contraindications are sufficiently clear that they require little more than mention. The usual

NORMAL VENOGRAM

1- SUP. SAG. SINUS
2- INF. SAG. SINUS
3- TRANSV. SINUS
4- STRAIGHT SINUS
5- GR. CEREBRAL VEIN OF GALEN
6- INT. CEREBRAL V.
7- BASAL V. OF ROSENTHAL
8- FRONT. ASC. V.
9- ROLANDIC V. OF TROLARD
10- PAR. ASC. V.
11- COMM. TEMP. V. OF LABBÉ
12- DESC. TEMPORO-OCCIP.

Figure 3.—Drawing showing the principal veins and sinuses.

contraindications to minor surgical procedures of an elective nature are generally contraindications to angiography. Further, when the diagnosis is certain, it should not be employed as a routine procedure in conditions for which surgical treatment cannot be of benefit—for example, thrombosis or hemorrhage in arteriosclerotic hypertensive vascular disease. On the other hand, it may be very important in the presence of clinical symptoms simulating those of progressive cerebral thrombosis when

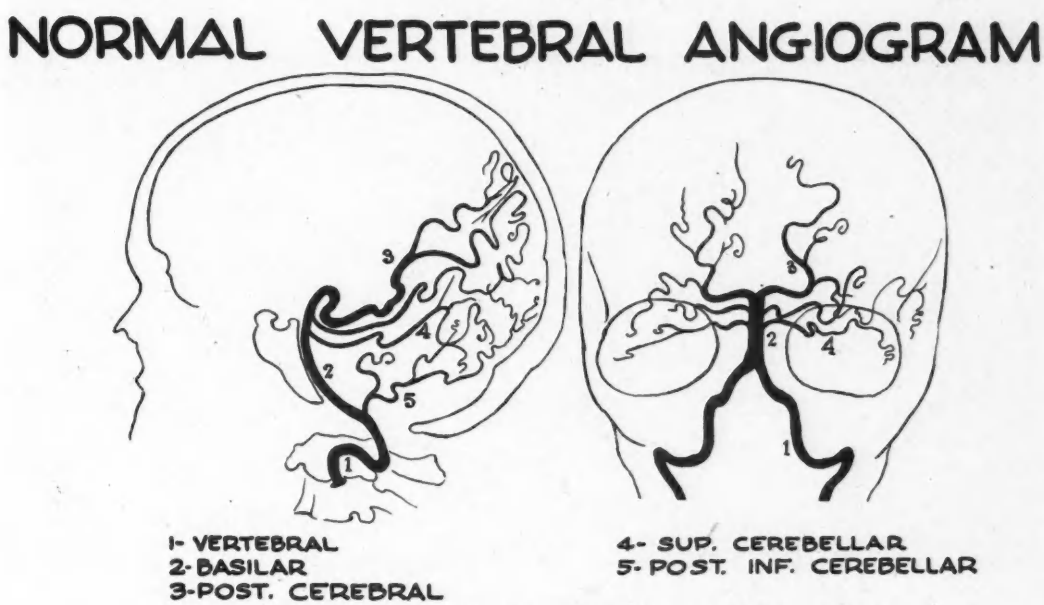

Figure 4.—Characteristic pattern of arteries demonstrable by vertebral arteriography.

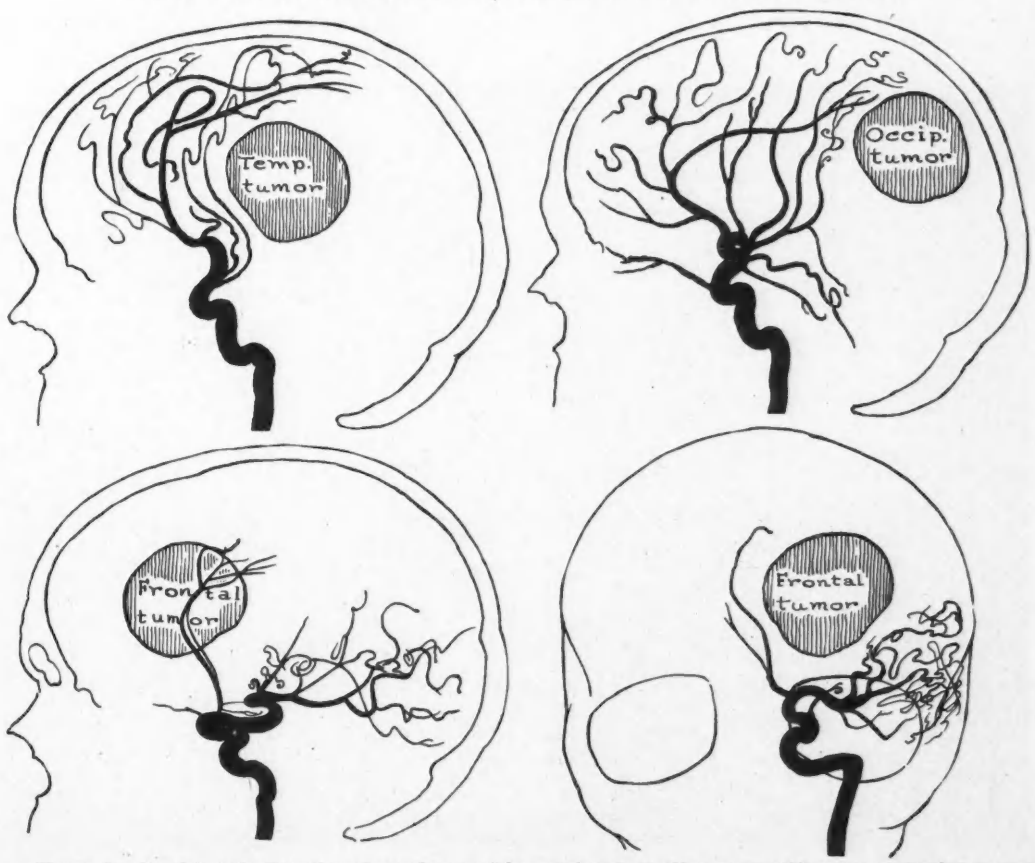

Figure 5.—Characteristic distortion of vessels caused by neoplasms or other comparable space-consuming masses within the brain.

Figure 6.—Angiogram showing capillary phase and concentration of dye in a typical meningioma. (a) Occipital artery feeding tumor. Extirpated tumor shown in insert.

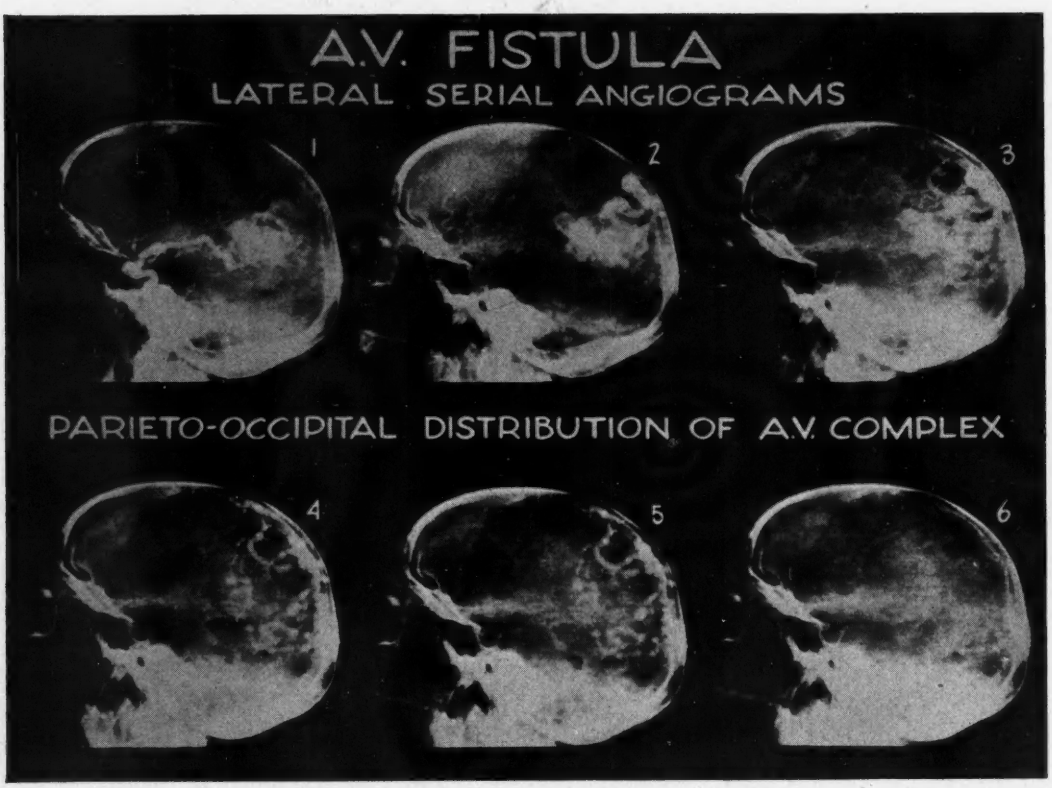

Figure 8.—Angiogram showing the dye concentrated in a typical arteriovenous malformation.

Figure 7.—Vertebral angiogram in a case of Lindau's disease. Dye can be seen concentrated in large hemangiomatous vascular sinuses. The angiogram discloses the location of these vessels, which is a great aid to the surgeon planning operation.

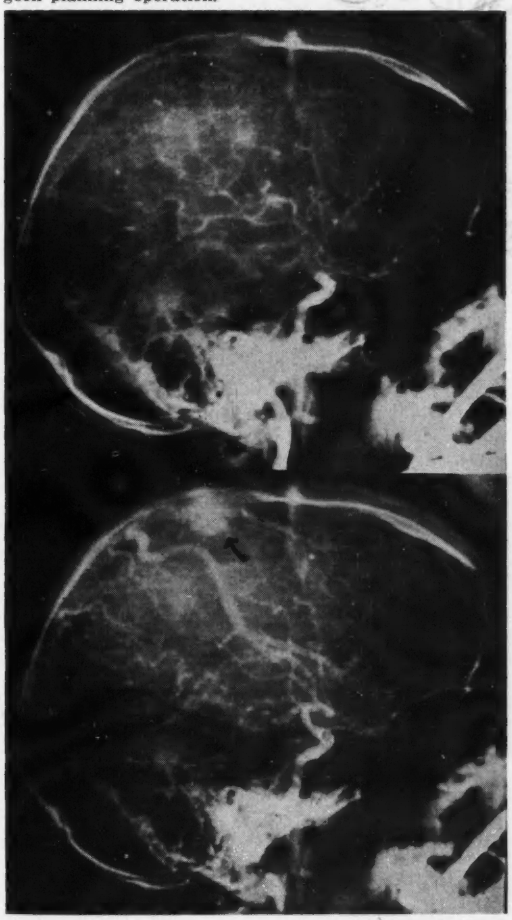

Figure 9.—Arrow points to typical telangiectatic lesion of the cerebral hemisphere that would have been missed entirely without controlled serial cerebral angiography.

hypertension and arteriosclerosis are not too pronounced. Neoplasms often produce such a picture.

PATHOLOGIC CHANGES

Intracranial space-consuming lesions, provided they are sufficiently large, tend to distort the normal arrangement of the vascular pattern. Lesions in the occipital region will usually cause a forward displacement of the vessels. Those in the frontal sector cause posterior or downward displacement, whereas others in the temporal zone cause an upward shift, etc. (Figure 5). These generalities are fairly constant provided the lesion is sufficiently large. However, the degree of displacement and of alteration depends on the size of the lesion and the lines of force it creates.

Neoplasms near the surface, in addition to their displacing qualities, usually have a blood supply of their own which offers a fertile field for angiographic investigation. Deep-seated tumors and especially those within the ventricles are ordinarily best demonstrated by pneumographic visualization. Malignant glioblastic tumors often have areas of necrosis and cyst formation in which an absence of vascularity is observed. In other areas, vascular proliferation is commonly visualized. Overlying convolutions are often widened, displacing the surface veins. Other tumors of the glioma group at times are said to show suggestive characteristic vascular changes. The classification of tumors by angiography, however, should certainly be exercised with caution and subjected to final microscopic verification. Angiography serves chiefly as a localizing agent and may reveal vascular structures which aid considerably in surgical planning.

Meningiomas cause distortion of the vascular system in a manner comparable to the changes caused by other space-consuming lesions. Since their blood supply is often from the external carotid artery, inclusion of this vessel in the angiogram is important. Dye can often be seen entering the tumor through the meningeal arteries. These tumors are ordinarily quite vascular; hence, the capillary phase of the angiogram frequently shows the tumor as a white mass resembling a snowball (Figure 6).

Tumors about the optic nerves or chiasm (for example, pituitary adenoma, craniopharyngioma, meningioma on the tuberculum sella, and optic nerve tumors) seldom present a diagnostic problem and can be recognized by the usual clinical means. Occasionally, however, unusual lesions are encountered and aneurysms must be considered. Therefore, angiography is frequently indicated in cases in which aneurysm in the area is suspected. Tumors of other cranial nerves can likewise be recognized by characteristic history and findings. The acoustic neuroma is probably the most common of these neoplasms and seldom presents diagnostic difficulty.

Rarely do tumors of the posterior fossa offer great difficulty in diagnosis. Angiomatosis retinae at times is associated with hemangioblastic tumors in the cerebellum, and in such instances angi-

Figure 10.—Angiogram showing location of typical pedunculated saccular arterial aneurysm.

ography may aid in the solution of technical problems before operation (Figure 7).

Intracranial arteriovenous malformations are not uncommon. When symptoms are present they are usually mild. Occasionally a bruit is audible over the scalp, but this is the exception rather than the rule. Pneumoencephalography rarely if ever gives conclusive information in such cases. Electroencephalography may establish which side the abnormality is on but never gives reliable information as to the character of the lesion. Angiography, however, establishes the diagnosis and location with certainty (Figure 8). Likewise, telangiectatic lesions can be demonstrated only by angiography. Furthermore, like other lesions they are liable to be missed entirely unless a complete serial angiographic study is done (Figure 9).

Congenital aneurysms are the most common cause of spontaneous subarachnoid hemorrhage. Therefore, unless clinical study shows hypertension,

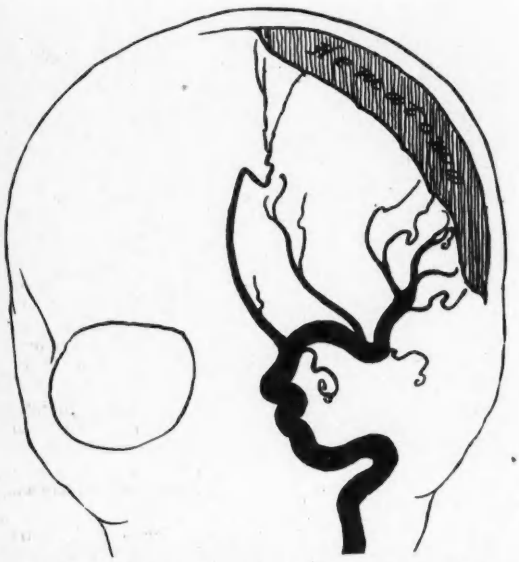

Figure 11.—Artist's drawing from an angiogram showing the vascular shift seen in the case of either subdural or extradural hemorrhage.

hemophilia, polycythemia vera, Dicumarol® intoxication, or other such conditions to be the cause of hemorrhage, angiography should be carried out. Often with with rest and conservative management the leaking will temporarily stop and all symptoms will clear. Some of the lesions are small and undoubtedly heal by thrombosis. Nevertheless, the majority of such aneurysms remain a potential cause of fatal attack unless demonstrated and repaired (Figure 10).

As a rule, angiography is not required for appraisal of lesions resulting from craniocerebral trauma. On the other hand, obscure post-traumatic states, such as chronic subdural hematoma, may be clarified by the procedure. These accumulations of blood cause a characteristic shift of the cortical vascular architectures away from the skull, and as a rule a general shift of the entire vascular pattern away from the lesion (Figure 11). Extradural hemorrhages usually have acute onset a few hours after injury and diagnosis seldom is difficult. Occasionally, however, angiography may be helpful.

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The Adaptation of Electroencephalography to Medicine

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SUMMARY

Electroencephalography is a valuable aid in diagnosis and prognosis of diseases affecting the brain. It has definite limitations.

Abnormal electroencephalograms are either paroxysmal or non-paroxysmal. Both of these changes may be generalized or focal.

Epilepsy is primarily associated with paroxysmal activity. Electroencephalography aids in the diagnosis and in determining the severity, course and response to treatment.

Non-paroxysmal activity, although less specific in pattern, indicates either generalized or focal pathologic change or some alteration of the normal structure of the brain. Non-paroxysmal activity may give supportive evidence referable to conditions, systemic or intracranial, which disturb the state of consciousness.

ELECTROENCEPHALOGRAPHY, which is a study of the electrical potentials of the cerebral cortex, has attained a degree of accuracy in dealing with diseases of the brain which is comparable to that of other laboratory procedures. It cannot, however, be considered a substitute for sharp clinical observation and sound clinical judgment.

Although the fundamental patterns of electrical energy emanating from the surface of the brain are relatively simple, the components entering into the formation of these pattern structures may be quite complex, and for this reason useful interpretation is dependent upon the skill of the electroencephalographer, who should have clinical experience as well as a grounding in physiology.

Briefly, the recording of electroencephalograms is carried out by means of electrodes which are attached in some convenient way to the scalp. The electrodes are placed in varying numbers over the five major areas of the brain, namely, frontal, motor, parietal, occipital and temporal areas. The waves picked up are amplified and are recorded in most instances on moving paper tape by means of magnetic ink-writing pens.

The recorded potentials from the cerebral cortex vary from 2 to 200 microvolts in amplitude and mostly occur within a frequency range of 1 to 30 cycles per second. The normal electroencephalogram has a dominant frequency which varies from 8 to 12 cycles per second and averages about 10 cycles. This frequency is called the "alpha" rhythm. A secondary group of waves ranging from 18 to 30 cycles per second is called the "beta" rhythm. (Figure 1.)

If this wave formation is considered with respect to the billions of neurons within the cerebral cortex, it becomes immediately obvious that potentials arising from each cell unite in some way so that they discharge in unison and appear on the tracing as a simple rhythm.

It is well then to consider both the spontaneous activity of cortical neurons and the associated synchronizing process. The electrical output of the neurons is related to the intrinsic metabolic process of the cerebrum. With an increase of metabolic activity the frequency of the brain waves is increased; conversely, a decrease in metabolic activity reduces the frequency of the brain waves.

Alterations in the environment of the cell which affect the state of its membranes, such as disturbances in ionic concentration, variations in interstitial fluid and the fluctuations of influent electrical impulses from remote regions, alter the individual neuronal pulsation. This alteration of the neuronal beat will appear in the electroencephalogram as a change in the rate of discharge, a distortion of the wave form and a variation in the amplitude of the wave.

It is postulated that the neurons of the cortex are held in synchronous beat one with another by so-called "pacemakers" which are located in areas, as yet undiscovered, deep within the substance of the brain.

If synchronization is increased the overall potential is increased and the frequency is more constant, but with reduced synchronization the cortical potentials disintegrate into a series of irregular, rapid and feeble oscillations. The waxing and waning (modulation) of the alpha rhythm in a well relaxed person exemplifies the regulatory control of the pacemakers. The destruction of cortical rhythm by opening of the eyes results from disturbance of the pacemakers.

Other factors remaining equal, the electroencephalograms from any one individual remain essentially the same from day to day. Differences between individuals may be quite extensive and yet remain within the known limits of normal. In one, the electroencephalogram is high in amplitude and regular in rhythm, in another, the rhythm is disorganized almost completely.

Deviations from the normal are manifested by

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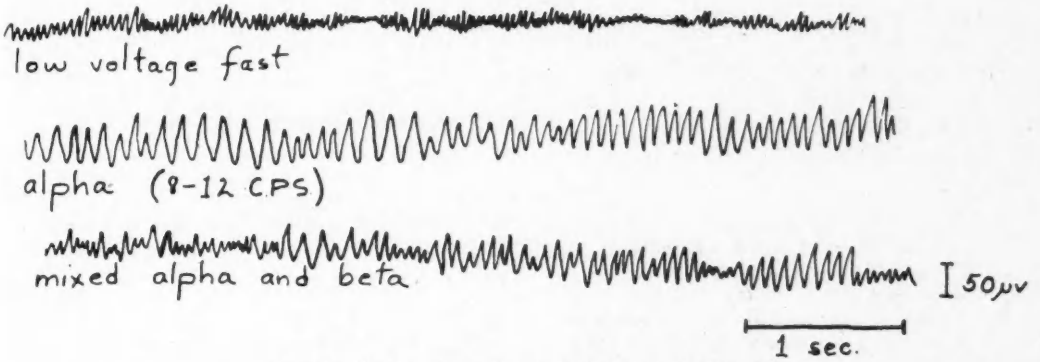

Figure 1.—Various types of normal electroencephalograms.

changes in amplitude and frequency. Factors directly or indirectly stimulating the cerebral cortex speed up the frequency of the electroencephalogram. Factors which act as cortical suppressors slow down the frequency of the electroencephalogram.

An abnormal electroencephalogram, then, may be one which is too fast, one which is too slow, or one which is both too fast and too slow. It may be continuous or paroxysmal, generalized or focal, mild or severe. It may be associated with a generalized or localized change in amplitude—either increased or decreased. Also, variations in wave form and pattern may accompany the shift in frequency.

Some of the factors influencing the normal electroencephalogram are:

Age. From infancy to the age of 13 or 14 years the frequency progressively increases until the average of 8 to 12 cycles per second has been reached. The rhythm slowly stabilizes and remains quite constant until the person is 35 or 40 years of age, at which time regularity and rhythmicity give way to irregular, low voltage, fast-and-slow waves.

Attention alters the rhythmicity of brain waves by influencing the synchronizing mechanism. With alertness the alpha rhythm may speed up slightly and the amplitude of the waves decrease. Superimposed low voltage fast waves may appear in the frontal regions. With reduction in attention by dozing or by decrease of alertness the basic frequency is retarded, and with the progression into light sleep slow waves appear which are interrupted by bursts of fast waves resulting from a reorganization of the pacemakers. As the depth of sleep increases, fast waves seem to disappear and there remain only random slow waves. With return to the waking state, the process is reversed.

Oxygen and Sugar. The brain maintains an equilibrium in its consumption of oxygen and sugar. A reduction of either of these substances in quantity or an inability of the cells to utilize the substances acts to suppress cellular function. The resulting electroencephalogram appears much as it does in sleep. As awareness is disturbed, the spontaneous waves become disorganized; with mild loss of consciousness, high amplitude slow waves mixed with low amplitude fast waves appear. As unconsciousness deepens, the frequency slows considerably and all fast activity disappears. There is a direct relationship between the wave frequency of the electroencephalogram and the level of consciousness.

Drugs that act as stimulators, such as caffeine, Benzedrine,® and strychnine, increase the frequency of the electroencephalogram. Drugs acting as depressants—that is to say, the barbiturates as a whole, paraldehyde, ether, alcohol, bromides, etc.—cause the electroencephalogram to slow in proportion to the depth of narcosis. (The initial stimulating effect of sodium amytal and sodium pentothal, however, results in an increase in frequency.)

Carbon dioxide. The effects of reduction of carbon dioxide are critical. Overbreathing, which is commonly encountered, introduces slow waves into the electroencephalogram in the majority of cases. Generally, the response to overbreathing is greatest in children, least in persons above forty years of age. In the presence of low oxygen tension and low blood sugar, the response to hyperventilation is exaggerated. Diagnostically, the response to hyperventilation is not considered significant in adults unless it is severe and in children unless it precipitates a slow wave-and-spike complex.

Abnormal electroencephalograms divide themselves into two distinct categories, those showing paroxysmal activity and those showing non-paroxysmal activity. For best clinical purposes the paroxysmal activity is associated with the epilepsies and allied disorders and the non-paroxysmal activity is associated with other pathologic conditions of the brain.

It is well to reemphasize that as it is the electrical activity of the cerebral cortex which is recorded on the electroencephalogram, abnormalities of the brain remote from the cortex are demonstrated in the electroencephalogram only if the cortex is affected by some commuted influence—whether this be through the interstitial fluids or via intercellular pathways.

Paroxysmal activity may be one that is too fast, the type found in grand mal epilepsy; one that is too slow, the type associated frequently with psycho-

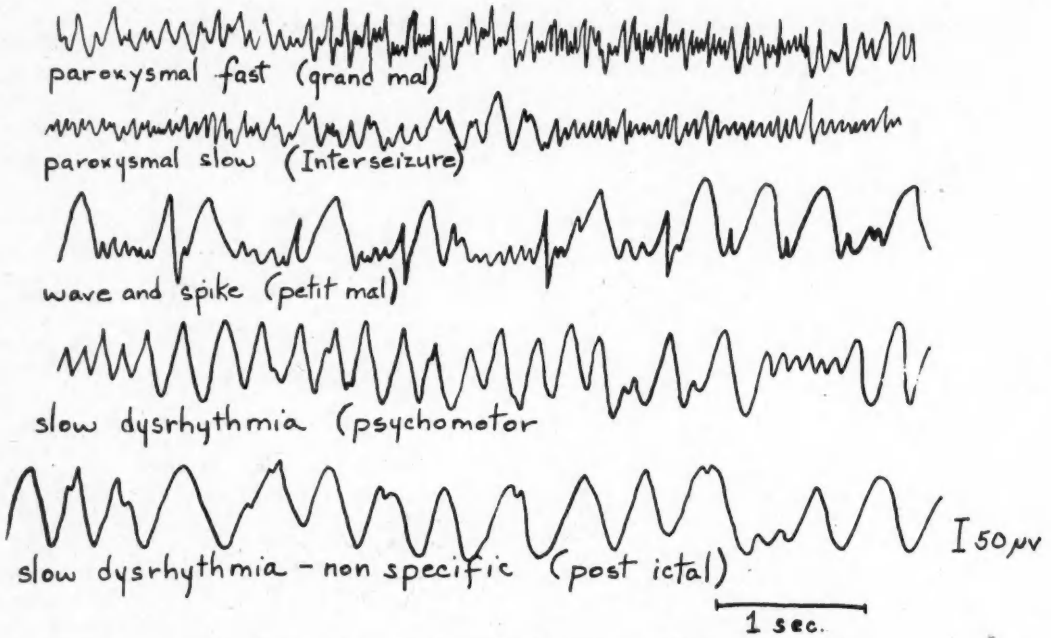

Figure 2.—Different types of waves during seizure and interseizure periods.

motor epilepsy; one that alternates between too fast and too slow (hump-and-spike wave), the type pathognomonic of petit mal epilepsy; or any combination of these three (Figure 2).

The origin of these wave patterns is obscure. They may appear over the entire cortex or symmetrically from two homologous areas which are discharging synchronously at a rate different from the remainder of the brain. They may "fire off" at a focus and remain focal or may spread over the cortex. There may be two or more foci discharging simultaneously, a situation which may lead to difficulties in interpretation.

Records of the seizure types are fairly consistent during the attack. Interseizure records range from completely normal to almost continuous dysrhythmia with patterns less obvious. Since the majority of electroencephalograms are taken during the absence of seizures, diagnosis is usually based upon the paroxysmal nature of the dysrhythmia rather than the pattern type. This, however, is not wholly true and much information can be gained by attempting to classify the interseizure dysrhythmia.

As to the reliability of electroencephalography in epilepsy, single recordings will show paroxysmal activity in about 40 per cent of cases and less well defined abnormality in about 20 per cent of cases, rendering the diagnosis fairly accurate in about 60 per cent of cases. As a working criterion, wave-and-spike activity is diagnostic; non-specific, paroxysmal activity is confirmatory; abnormal fast or slow, more or less non-paroxysmal activity is suggestive of epilepsy. Serial recording over a period of time increases the percentage of accuracy.

Predisposition to a convulsive disorder is suggested by the fact that near relatives of epileptic children have electroencephalographic abnormalities nine times more frequently than near relatives of normal children. Twenty-eight per cent of children with epileptic parents or near relatives have cerebral dysrhythmia without having demonstrable seizures. In convulsion-susceptible identical twins, both are expected to have comparable dysrhythmia, although only one may have seizures. In similar twins who are not convulsion-susceptible, symptomatic epilepsy may result from cerebral trauma. The injured twin may have dysrhythmia while the uninjured may not.

Electroencephalography has become useful in following the course of epileptic patients under treatment. The paroxysmal activity increases with the approach of a seizure and is relatively silent during the interseizure period. Anticonvulsant drugs do not inhibit dysrhythmia but do reduce it to a degree. Periodic checking will often reveal the anticonvulsive effect of the therapeutic agent on the patient.

Dysrhythmia associated with latent convulsive disorders may be brought out by recording electroencephalograms during sleep. In psychomotor epilepsy, spikes which are suppressed during the waking state appear in the anterior portions of the temporal lobes during sleep.

Non-paroxysmal abnormality is less specific than paroxysmal. The abnormality may be generalized (Figure 3) indicating an involvement of the cortex as a whole, or it may be focal (Figure 4). It may be fast or slow. Fast activity implies stimulation of the cortex and slow activity suppression. The cortex

is more responsive to acute disturbances. As the condition becomes chronic, the cortex tends to adjust itself and reestablish its rhythm, so that the electroencephalogram may be normal even though clinical symptoms persist and there is evidence of permanent damage. Corollary to this is the relationship of the electroencephalographic change with the level of consciousness. In the presence of delirium (which may be induced by a number of conditions such as generalized systemic disturbance of metabolism, anoxia, hypoglycemia, fever, nutritional deficiency, and drug intoxication) or in the presence of generalized intracranial involvement by infectious, vascular disorders, brain softening and degeneration, brain edema or internal hydrocephalus, the electroencephalogram shows high voltage random slow activity mixed with fast waves of moderate amplitude. The dominance of slow activity over fast is related to the acuteness of the delirium, the depth of stupor and the severity of cellular involvement. As the delirium subsides, the slow random activity becomes less pronounced and fast waves more prominent until, with the disappearance of delirium, the electroencephalogram approaches normal. As the disease process becomes chronic, the cerebral cortex tends to reestablish its rhythm and the electroencephalogram then will not reveal the residual pathologic condition.

Some of the diseases showing acute generalized electrical involvement of the cerebral cortex are: systemically, general infections, cardiovascular-renal diseases with cerebral involvement, and metabolic disorders; intracranially, encephalitis (all forms), syphilis of the central nervous system, cerebral trauma, meningitis, hemorrhage, thrombosis and demyelinizing diseases. The electroencephalogram is abnormal in Sydenham's chorea only if the cortex is involved. Diseases of the basal ganglia, such as Parkinsonism, do not alter the electroencephalogram. Subdural hematoma, unless the brain is displaced, may produce a mild depression of amplitude without otherwise altering the electroencephalogram.

During the course of these diseases a latent convulsive disorder may be released or activated and a paroxysmal dysrhythmia appears in addition to the generalized non-paroxysmal activity.

If the cortex is directly involved, local pathologic changes in the brain are revealed as an electrical focus. Some of the conditions most readily diagnosed and localized are tumors such as meningiomas, metastatic lesions, acute vascular accidents, local trauma, and abscesses. Of these lesions, abscesses lend themselves to diagnosis more readily than the others.

Deep lesions, such as infiltrating gliomas, thromboses, hemorrhages and local areas of demyelinization in the white matter of the brain, can be localized only if there is interruption of the subcortical pathways involved in maintaining normal cortical rhythm. Deep midline lesions involving the corpus callosum often bring about a bilateral symmetrical

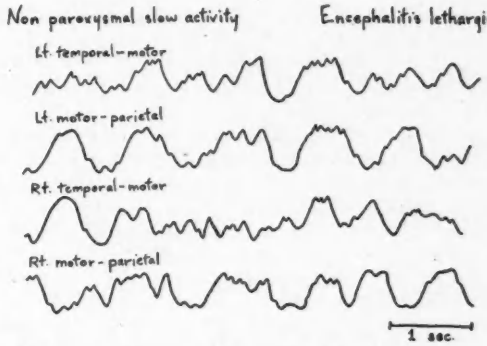

Figure 3.—Random, slow activity seen in acute conditions of the brain frequently associated with disturbance of consciousness.

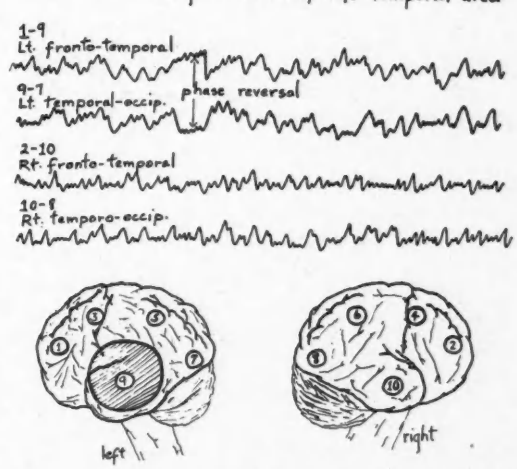

Figure 4.—Focal slow activity in this case results from interruption of subcortical fibers to the left of the temporal area.

abnormality of the electroencephalogram which resembles that of the diffuse involvement of the cortex in delirium.

Lesions below the tentorium, for practical purposes are not amenable to localization by the electroencephalogram.

Because of the sensitivity of the electroencephalogram to the degree and intensity of cortical dysfunction, serial recordings may be most helpful in following the course of intracranial disease. It becomes useful in differential diagnosis. On the one hand, early, minor disintegration of the normal alpha rhythm from one hemisphere which progressively becomes slower and which ultimately (in a few months) develops into a slow wave focus in one of the major areas of the hemisphere suggests strongly the presence of an expanding space-occupying lesion. On the other hand, a rather acute and active focus which shows a shifting toward normal

describes a lesion, such as a thrombosis, which is resolving. Local abnormalities in the case of multiple sclerosis appear and disappear with exacerbations and remissions of the disease. The slowing of the waves is coordinated with edema.

In some instances, electroencephalography has a degree of legal status. Some of the indications are controversial but in general the presence of paroxysmal activity supports the clinical impression of epilepsy. Residual abnormalities after a three-month post-concussion period are strong evidence of permanent brain damage. Negative findings are less convincing because it is recognized that the brain adjusts to chronic disorders and will reestablish its basic rhythms, thereby presenting a normal electroencephalogram in the presence of unchanging brain damage. The presence of local pathologic changes can at times be revealed through the use of accessory techniques, such as induced sleep and cerebral stimulation by Metrazol,® which may activate damaged tissue that under normal conditions is electrically inactive.

Functional disorders such as psychoneurosis, psychosis, personality disturbances, etc., at present do not show abnormalities in the electroencephalogram sufficient to be diagnostic. Further investigation promises some clarification in these conditions which may help the clinician.

Diagnostic Contributions of the Electromyogram

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SUMMARY

When muscles contract, they generate electricity. This muscle electricity can be seen and heard on the electromyograph. Normal muscles generate a different type of electrical impulse than do paralyzed muscles, and for this reason the electromyograph is of great assistance in the diagnosis, prognosis and treatment of such conditions as poliomyelitis, nerve injuries and strokes.

ELECTROMYOGRAPHY is the science which treats of the recording and measurement of the voltages generated by normal and abnormal muscles. In order to record and measure muscle voltages accurately, it is first necessary to elicit them from a muscle by means of a needle electrode in the muscle. Next these minute voltages must be amplified many times and then converted into visible patterns and sound energy by means of a cathode ray oscillograph and loud speaker. The instrument which elicits, amplifies, and converts the muscle voltages into visible patterns and sound energy is called an electromyograph (Figure 1) and the permanent record of the muscle voltages, which is obtained by photographing the visible patterns on the cathode ray oscillograph, is called an electromyogram. When interpreted correctly, electromyograms are a useful adjunct to the neurological examination in assessing the functional integrity of the neuromuscular system.

Relaxed normal voluntary muscle generates no voltages which can be recorded by the electromyograph. In other words, a completely relaxed normal voluntary muscle is an "electrically silent" one from the electromyographic standpoint. Normal voluntary muscle which is made to contract as a result of either voluntary or reflex effort generates what are termed "normal motor unit voltages."

A motor unit has been defined by Denny-Brown and Pennybacker[3] as a functional unit consisting of one anterior horn cell together with its axon and the 100 to 150 muscle fibers which the axon innervates. When the axon of such a motor unit is excited, all of the muscle fibers appear to contract synchronously, and as a result of the spread of the contraction wave, a simple (monophasic, diphasic, or triphasic) voltage is generated.

Normal motor unit voltages range in magnitude from about 100 to 2,000 microvolts and are readily elicited from all areas of the contracting normal muscle. The duration of a single wave is of the order of 3 to 10 milliseconds, and the repetition frequency varies from about 5 to 30 per second, depending on the force of contraction. Because of their simple wave form and relatively long duration, normal motor unit voltages produce a very characteristic thumping noise in the loud speaker.

When voluntary muscle has been deprived of its nerve supply or denervated for various periods of time, depending upon the species, the individual denervated muscle fibers begin to twitch in a rhythmic manner. This rhythmic twitching of denervated muscle has been termed denervation fibrillation and, according to Denny-Brown and Pennybacker,[3] results when the denervated muscle fibers become sensitized by neural atrophy to small amounts of acetylcholine in the normal circulation. Since the term denervation fibrillation denotes the involuntary contractions of individual muscle fibers, it is of great importance to note that true denervation fibrillation cannot be observed clinically through the intact skin. In order, therefore, to detect and prove its presence in a muscle, it is necessary to employ electromyography. The voltages generated by fibrillating denervated muscles are termed denervation fibrillation voltages and range in magnitude from about 5 to 100 microvolts. They usually have a diphasic wave form, and their repetition frequency varies from about 2 to 30 per second. A single wave has a duration of only 1 to 2 milliseconds, and because of its extremely short duration, a fibrillation voltage produces a very characteristic clicking noise in the loud speaker.

When a denervated muscle becomes reinnervated —that is, when it again acquires nerve substance through regeneration of its own nerve—it generates motor unit voltages which are highly polyphasic or complex in wave form. Because Weddell and associates[7] observed these highly complex motor unit voltages in muscles during the early stage of reinnervation after peripheral nerve lesions, they designated them as "nascent" motor unit action potentials or voltages. In a later communication, these investigators[8] stated that they believed the term "nascent" to be an inaccurate one because they thought it theoretically possible to have highly polyphasic or complex motor unit voltages during the course of demyelinating diseases. Other investigators[4] recently reported that complex motor unit voltages are a constant finding in muscles following poliomyelitis and in such degenerative diseases as amyotrophic lateral sclerosis and progressive muscular atrophy. From these observations, they have concluded that highly polyphasic or complex motor unit voltages are abnormal electromyographic

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phenomena and as such may represent either early nerve degeneration or early nerve regeneration.

It was pointed out previously that the muscle fibers of a normal motor unit contract synchronously, thus producing a simple motor unit voltage. The muscle fibers of an abnormal motor unit, on the other hand, appear to contract asynchronously, thus producing a complex or highly polyphasic motor unit voltage.

Complex or abnormal motor unit voltages range in magnitude from about 1,000 to 1,500 microvolts. Their repetition frequency varies from about 2 to 30 per second, and the duration of a single wave group is usually in the range of 5 to 15 milliseconds. Because of the complexity of these waves, abnormal motor unit voltages give rise to a very rough sounding noise in the loud speaker.

Most clinicians usually associate fibrillary twitchings of muscles with such degenerative diseases as amyotrophic lateral sclerosis and progressive muscular atrophy. The electromyographist, however, prefers to designate such visible involuntary contractions as fasciculations and to reserve the term denervation fibrillation for the invisible involuntary contractions of individual denervated muscle fibers. From the electromyographic standpoint, a complex fasciculation voltage simply represents the involuntary contraction of an abnormal motor unit. The characteristic voltages generated by normal, denervated and partially denervated muscles are illustrated in Figure 2.

It should be emphasized that denervation fibrillation is a phenomenon characteristic of denervated muscle, and for this reason denervation fibrillation voltages are not elicited from a muscle unless Wallerian degeneration of the nerve supply has taken place. Because of this fact, denervation fibrillation is a valuable objective sign of lower motor neuron disease. This is true because it is a constant finding following known lesions of the final common path and one that can neither be controlled by the patient nor observed clinically through the intact skin by the physician. When recorded electromyographically, however, its presence aids greatly in differentiating between upper and lower motor neuron disease,[1] myopathy and atrophy,[8] and functional and organic paralyses.[4] (Any precise objective test finds wide application in medicolegal fields, and electromyograms obtained by photographing a cathode ray oscillograph have been accepted as evidence in both federal and superior courts in California.)

The presence of denervation fibrillation can be of use in localization.[2,6] If for example, an upper extremity is examined and denervation fibrillation is noted only in those muscles receiving innervation from the median nerve, the electromyographic findings are consistent with a lower motor neuron lesion of the median nerve. In addition, it may be concluded that a certain percentage of the axons have undergone Wallerian degeneration. If on the other hand, the distribution of the denervation fibrillation corresponds to the distribution of the 7th cervical root, the electromyographic findings are consistent with a lower motor neuron lesion involving the 7th cervical root. Depending on the percentage of muscle fiber fibrillation, it can be further concluded that the electromyographic findings are consistent with the patient's complaints of paralysis, paresis, or fatigability. In order to express an opinion, however, concerning the cause of the peripheral nerve or root lesion, the electromyographic findings must

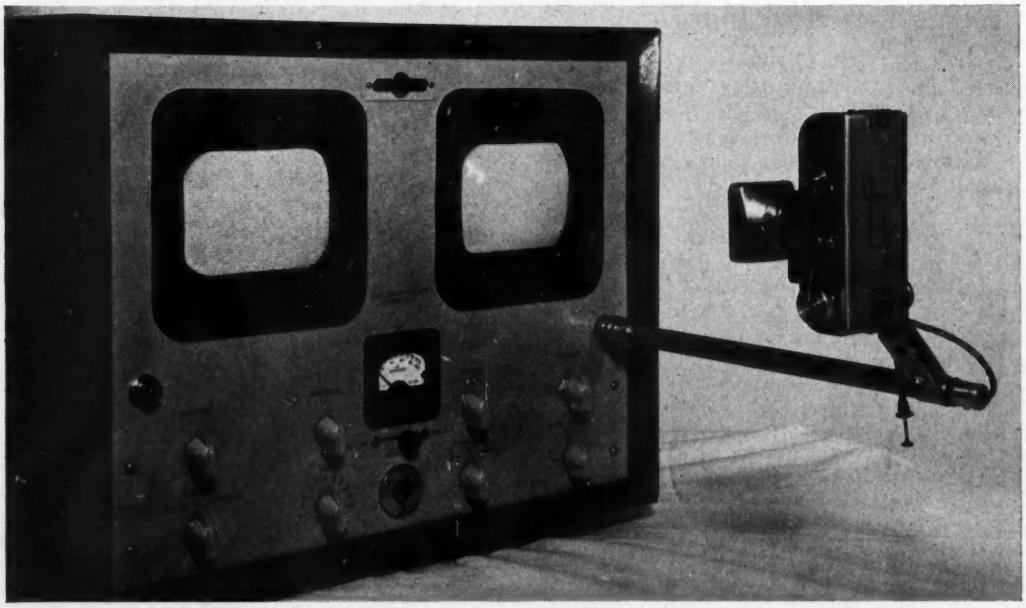

Figure 1.—Electromyograph, consisting of amplifiers, cathode ray oscillograph, loud speaker and camera.

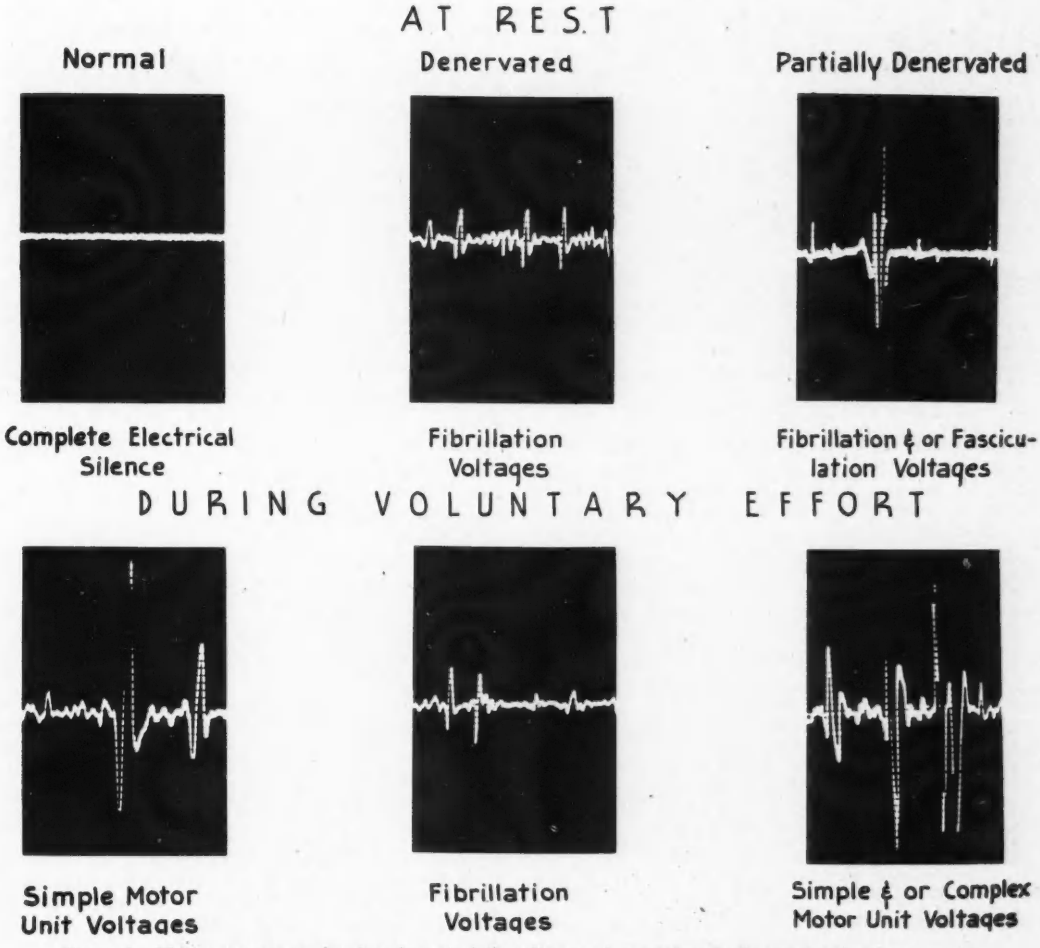

Figure 2.—Electromyograms, showing characteristic voltages of normal and abnormal voluntary muscle.

be correlated with a careful history and clinical examination.

While it is true that the presence of denervation fibrillation in a muscle indicates that some of the muscle fibers are completely denervated, it likewise indicates that these muscle fibers are still contractible tissue and capable of reinnervation once a nerve regenerates to them. This fact is very helpful in forming a prognosis relative to either ultimate functional recovery or ultimate permanent disability. When, however, an appreciable amount of denervation fibrillation in a muscle is noted, these muscles should receive vigorous physical treatment in the form of interrupted galvanic stimulation combined with heat and massage to prevent irreversible fibrotic changes and consequently a poor functional result.[5] A case in point is the patient with fracture and concomitant peripheral nerve lesions, who because of extensive wasting and fibrosis of the muscles is unable to use the injured limb even though the bones heal well.

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CASE REPORTS

- Primary Spindle-Cell Sarcoma in the Right Auricle
- Hematuria Following Ingestion of Pyribenzamine Hydrochloride
- Familial Occurrence of Polycythemia and Leukemia

Primary Spindle-Cell Sarcoma in the Right Auricle

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PRIMARY malignant tumors of the heart are rare, approximately 100 having been reported in the world literature to date.[12] Perlstein,[6] in an excellent review in 1918, collected reports of 31 cases and demonstrated the characteristics of the clinical and pathological syndrome produced by these tumors, namely, the multiplicity of symptoms and findings which do not fit the pattern of any common form of heart disease, and the frequent origin of these neoplasms in the right auricle. Bodenheimer,[2] who reported the first primary malignant cardiac tumor in 1865, well stated the clinical problem: "One can think of heart tumor when history, clinical examination, and observation do not speak for any other heart disease, when the symptoms occur rather suddenly and unexpectedly and the condition soon takes a faster, soon a slower course." Five cases of malignant cardiac tumors have been correctly diagnosed during life.[3, 7, 8, 9, 11] A few probable rhabdomyosarcomas have been reported.[1, 2, 4] Mahain[5] recently extensively surveyed the literature on all types of primary cardiac tumors and his studies of the sarcomas led him to conclusions similar to those previously mentioned.

CASE REPORT

The patient, a Mexican male 25 years of age, had been well until seven days previously. Then, while running to catch a streetcar, he noted for the first time an empty sensation in the epigastrium and slight shortness of breath. These symptoms persisted even without exercise, and three days later there developed substernal "heaviness" which seemed to ascend into the neck and which was associated with what the patient described as a "ball in the throat." The dyspnea and substernal oppression became progressively more severe. During the first five days following the onset of symptoms, the patient continued to work as a cement worker, but two days before admission to the hospital the symptoms became so severe that he was required to cease work. No other symptoms were elicited, and no further details referable to the present illness could be obtained from the patient.

Physical Examination: The temperature was 98.4° F., the pulse rate 130 and respirations 36 per minute. The blood pressure was 104 mm. of mercury systolic and 86 mm. diastolic in both arms. The patient was well developed, well nourished, alert, cooperative, mildly orthopneic, and apparently dyspneic.

Definite venous distention was noted in the neck. There was no tracheal shift and no enlargement of the thyroid gland.

The chest was symmetrical, with bilaterally equal respiratory movements, and there was no apparent deformity. On percussion, bilateral dullness was noted below the eighth thoracic spine posteriorly, and there appeared to be no descent of the diaphragm on deep inspiration. There was a suggestion of a change in dullness, with a shift to either lateral decubitus position. Breath sounds were diminished over this same area of dullness, with somewhat more diminution on the right side than on the left. Voice sounds were diminished over the same area. Moist inspiratory rales were noted over both bases; they were louder on the left.

The apex of the heart was approximately 2 to 3 cm. to the left of the midclavicular line in the sixth intercostal space, and dullness to percussion indicated that the right border was approximately 1 cm. lateral to the right sternal border in the fourth intercostal space. The heart sounds were very distant, and no murmurs, thrills, or rubs were noted. The rhythm was regular, and the pulmonic second sound was greater than the aortic second sound.

The liver was palpable 3 cm. below the right costal margin. The edge was smooth and the entire liver was slightly tender to deep palpation. No other organs were palpable, and no further abnormalities were noted.

Hemoglobin content of the blood was 14 gm. per 100 cc. Erythrocytes numbered 4.51 million and leukocytes 10,250 per cubic mm. Results of Wassermann and Kahn tests were positive. The packed cell volume was 40 mm. Corrected sedimentation rate (Wintrobe) was 0.0 mm. in one hour. Results of urinalysis were within normal limits.

Bilateral pleural effusions, with evidence of associated mediastinal or small pericardial effusion, were noted on an x-ray film of the chest (Figure 1).

Sinus tachycardia (120 per minute), with electrical alternans, was recorded upon an electrocardiogram. The tracing was consistent with that commonly observed in acute pericarditis.

Venous pressure was 380 mm. of water, and manual pressure over the liver caused the fluid in the manometer to go over the top (over 400 mm.).

Circulation time, arm to lung, was 10.5 seconds using 1 cc. of ether intravenously, and arm to tongue was 30 seconds using 6 cc. of sodium dehydrocholate (Decholin®).

The cardiac silhouette on a teleroentgenogram was of "water bottle" type and there was pronounced, generalized enlargement on fluoroscopy. Cardiac pulsations and vascular indentations were almost completely absent. In addition, the basal silhouette of the heart appeared broadened. The findings were consistent with clinical diagnosis of pericarditis with effusion.

Clinical Impression: (1) Possible rheumatic fever or other hyperergic disease with pleural, pericardial, and possibly peritoneal involvement. (2) Possible acute myocardial infarction.

The initial treatment consisted principally of oxygen in-

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halation, sedation, and salt restriction. On the second hospital day the patient rapidly became extremely dyspneic. The blood pressure was 120 mm. of mercury systolic and 85 mm. diastolic. A right thoracentesis was performed, and following the removal of 350 cc. of clear straw-colored fluid the patient fainted. Prompt recovery occurred after inhalation of ammonia fumes. Specific gravity of the pleural fluid was 1.013, and the total protein content was 2.3 gm. per 100 cc. Smears and cultures were negative for all organisms including Mycobacterium tuberculosis. An electrocardiogram showed sinus tachycardia (108 per minute) and the other changes which were consistent with acute pericarditis with effusion.

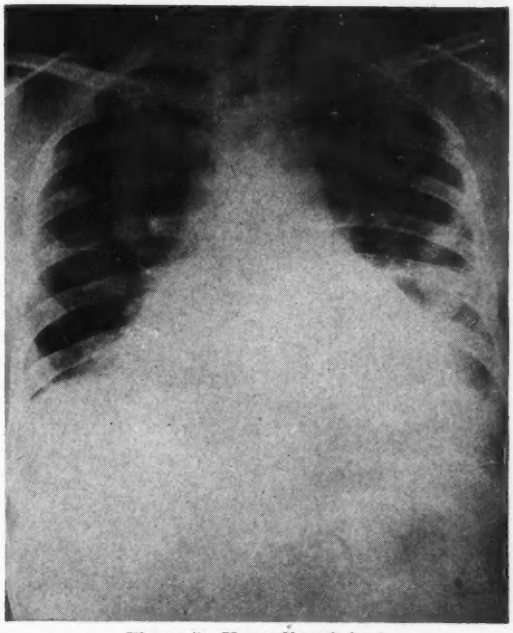

Figure 1.—X-ray film of chest.

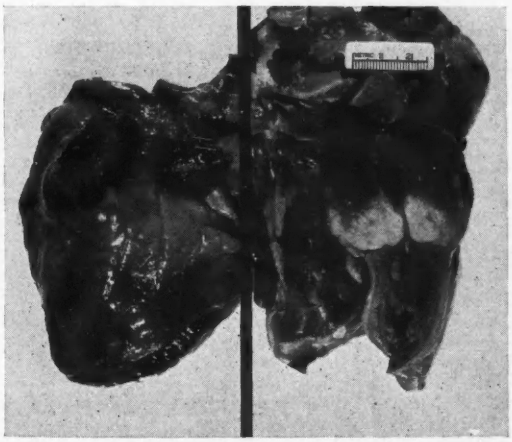

Figure 2.—*Left:* Neoplasm in right auricle with ulceration of its epicardial surface. *Right:* Hemisection through tumor showing hemorrhagic upper segment and the grayish yellow lower part with extension toward the insertion of the tricuspid valve.

On the fourth hospital day the patient became progressively more dyspneic. Left thoracentensis was performed, and 500 cc. of clear straw-colored fluid, with a specific gravity of 1.012 and a total protein content of 1.8 gm. per 100 cc., was removed. A right thoracentesis yielded 1,050 cc. of similar fluid. Later, left thoracentesis was repeated and 350 cc. of fluid was drawn. Mild syncope followed the procedure. At the conclusion the pulse rate was 86 per minute and the blood pressure 102 mm. of mercury systolic and 60 mm. diastolic. Although apprehensive, the patient was less dyspneic.

The patient died on the fifth hospital day after a night of progressively increasing dyspnea.

The patient was afebrile during his entire hospital stay.

At autopsy, seven hours after death, the only abnormalities noted on external examination were diffuse cervical edema typical of "bull neck" with distention of the cervical veins. No peripheral edema was present.

The pericardium was tautly distended with 1,150 cc. of bright red fluid having specific gravity of 1.030, which arose from the ulcerating, necrotic, deep red surface of a tumor mass in the body of the right auricle (Figure 1). The growth at its base measured 3 x 5 cm. and at its necrotic apex was 2 x 2.5 cm. The endocardium of the right auricle above the neoplasm was normal, but cutting 2 mm. into the endocardium of this area exposed the yellowish color of the tumor parenchyma. The right auricle was not dilated and the appendage was normal. The heart, with the growth, weighed 320 gm. Valve leaflets and chorda tendineae were normal. Valve circumferences were: Mitral 9 cm., aortic 7 cm., pulmonic 6.5 cm., and tricuspid 11 cm. The left ventricular wall measured 13 to 15 mm. and the right 2 to 5 mm. The chambers were not dilated. Coronary arteries were normal. Section through the long axis of the tumor showed it to be limited entirely to the auricular myocardium with extension to the insertion of the tricuspid valve (Figure 2). The tumor measured 3 x 5.5 cm. The inferior 2 x 3 cm. area of neoplasm consisted of grayish yellow material of firm consistency. The tissue above this was deep red in color and of mushy consistency. There was no evidence of metastasis of the tumor to other areas in the myocardium or to other organs.

Each pleural cavity contained 1,100 cc. of straw-colored fluid. The right lung weighed 1,050 gm. and the left 900 gm. The left lower lobe sank on immersion in water. Yellowish, foamy edematous fluid filled the tracheobronchial tree. The cut surface of the lung parenchyma was deep red in color, with rolled edges, and the surface still glistened after scraping. The lower border of the liver was at the costal margin and the organ weighed 1,400 gm. It was normal on the surface. On section it was noted to be grayish brown with increased lobular markings. No abnormalities were noted in gross and microscopic examinations of brain, meninges, thyroid, adrenal and pituitary glands, testes, entire gastrointestinal tract, pancreas, biliary system, kidneys, bone marrow, psoas muscle, rectus, and sternocleidomastoid muscles.

The parenchyma of the tumor consisted of moderately anaplastic pleomorphic spindle-shaped cells with deeply basophilic pleomorphic nuclei. The cells were loosely packed and tended to grow in parallel chains (Figure 3). Nuclei were not prominent. Lymphocytes infiltrated between some cords of neoplastic cells. In other areas clumps of lymphocytes were present. The growth at its margin invaded between normal muscle fibers. Scattered areas of fibrosis were present throughout. The central part contained areas of necrosis with polymorphonuclear and mononuclear infiltration. There were rare giant cells present which did not contain concentric striations. The upper part

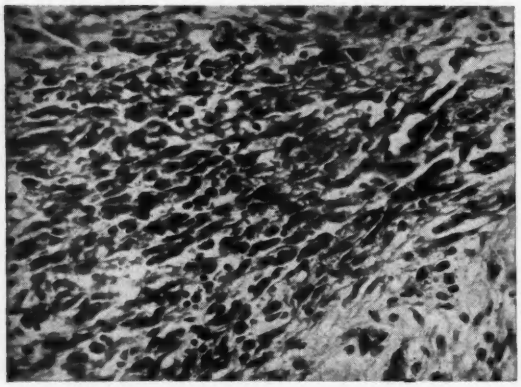

Figure 3.—Section through parenchyma of tumor showing spindle-shaped cells and fibrous stroma.

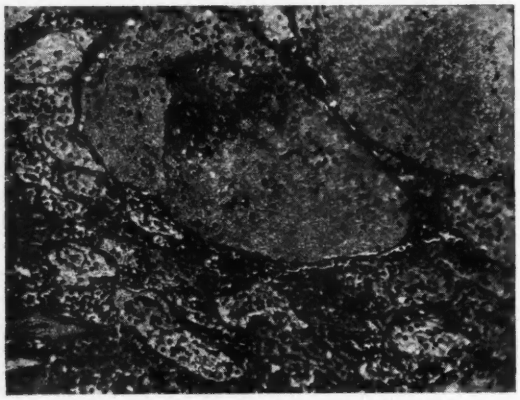

Figure 4.—Hemangiomatous upper section of tumor.

of the lesion was very vascular and resembled a hemangioma (Figure 4). Several tumor thrombi invaded the veins (Figure 5). With Von Gieson stains the tumor cells appeared yellowish pink and there was no connective tissue between them. There were moderate amounts of argentaphilic fibers about the tumor-cell bundles. No transverse striations were noted on Von Gieson stained specimens nor when hematoxylin and eosin, phosphotungstic acid and hematoxylin, or polaroid microscopy were used. Longitudinal fibrils were not demonstrated by phosphotungstic acid and hematoxylin stain. Patchy bronchopneumonia and pulmonary edema were noted upon section of the lungs. There was central congestion with atrophy of central liver cells and hemosiderin pigmentation in them.

DISCUSSION

Spindle-shaped cells such as made up the tumor parenchyma in this case are commonly noted in the reports of rhabdomyosarcoma of the heart, and giant cells are also common in this condition. The presence of tumor thrombus in the vein is characteristic of sarcomata. The giant cells in peripheral muscle rhabdomyosarcoma, however, have concentric striations, which were not found in the case here reported.

The Los Angeles Tumor Registry interpreted the neoplasm as being a "spindle-cell sarcoma in the right auricle."

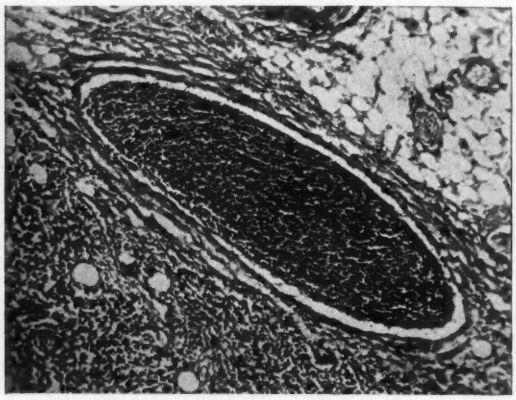

Figure 5.—Tumor thrombus in vein.

Concerning the diagnosis of rhabdomyosarcoma, MacCollum, as quoted by Larson and Sheppard,[3] stated very aptly: "Since the criterion demanded before an origin from muscular tissue will be admitted is the demonstration of characteristic cross-striations, it is not at all improbable; indeed it is almost certain that many tumors truly of such origin or character are not recognized as such, and are relegated to the tumor scrap heap of sarcoma."

SUMMARY

In a case of spindle-cell sarcoma in the right auricle there was some suggestion that the tumor was of muscle origin.

5720 Wilshire Boulevard.

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Hematuria Following Ingestion of Pyribenzamine Hydrochloride

Report of a Case

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WITH the widespread use of antihistaminic drugs, reports of toxic side-reactions have been increasing. Gastrointestinal and cerebral reactions predominate. In one of the most recent reports, Wolfson[3] noted urinary system disturbances following ingestion of pyribenzamine hydrochloride, with no gastric or cerebral reactions. In that case, the symptoms of diminishing urinary stream and increased bladder pressure, in the absence of any abnormalities in the urinary elements, indicated transient obstruction, probably in the region of the bladder neck.

A patient observed by the author had gross blood in the urine, associated with bladder pain, frequency and nocturia, after taking pyribenzamine hydrochloride.

CASE REPORT

A white male, aged 32, had been under observation and treatment for six months for chronic, non-specific prostatitis. Complete studies had indicated that there was no disease in the kidneys, as evidenced by normal intravenous pyelograms. In cystourethrograms taken several months before no abnormalities had been noted. In an effort to clear the prostatic infection, foci elsewhere were searched for. Chronic ethmoid sinusitis was present; and an otolaryngologist who, in consultation, diagnosed the condition as of allergic origin, treated the patient with sinus washings and then advised pyribenzamine hydrochloride in doses of 50 mg. four times a day. Two days after treatment with the antihistaminic agent was started, gross hematuria occurred. Associated with it were bladder pain, frequency of urination every 20 minutes during the day and hourly at night. The urine was grossly rust-colored, the reaction to a chemical test for blood was strongly positive, and innumerable erythrocytes per high-power field were noted in microscopic examination. Upon physical examination, no other toxic side-reactions were noted and no other condition that might cause the bleeding. The urethra and prostate were normal to palpation, as were the vesicles. Tenderness in the bladder was noted on deep palpation. The pyribenzamine was discontinued and urinary sedatives and antispasmodics were given. The following day, the bleeding was considerably diminished, but the urine still contained 50 to 60 erythrocytes per high-power field. There were no leukocytes. Reaction to a test for blood was 3+, and for albumin 2+. Within five days the symptoms had fully abated and the urine was microscopically normal.

DISCUSSION

The case reported is another in which urinary disturbances were noted following administration of pyribenzamine hydrochloride. In the previously reported case,[1] dysuria and increased frequency ceased in one day following discontinuance of the drug. In the present case, however, there was true hemorrhagic cystitis without actual infection. The mechanism was probably purely an irritative phenomenon. The author believes it likely that the excretion of the drug in the urine, in sensitive subjects, causes edema and exudation of the bladder mucosa, especially in the trigone region, much in the way that the formaldehyde of urotropin breakdown causes these conditions in the bladder of sensitive subjects. Wolfson[3] in his report indicated that "the antihistaminic may possess a spasmogenic property heretofore unrealized."

It would seem to be worth while for physicians giving pyribenzamine hydrochloride to question patients more frequently and more carefully with regard to urinary discomforts so that these complications may be avoided.

SUMMARY

The case reported is one in which gross blood appeared in the urine, with frequency, nocturia and bladder pain, following ingestion of pyribenzamine hydrochloride.

9615 Brighton Way.

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Familial Occurrence of Polycythemia and Leukemia

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THE existence of polycythemia in two or more members of a single family has been reported by several observers, and in 1933 the cases previously reported in the literature were reviewed by Spodaro and Forkner,[15] who found six studies of what they believed to be proven familial polycythemia. These examples are cited briefly below.

Bernstein[2] described a polycythemic patient whose son had an erythrocyte count of 7.5 million and whose father, who died at the age of 47, had had a high color. In a family reported upon by Doll and Rothschild,[5] five members had Huntington's chorea; two of the five also had erythrocyte counts of six million or over, and one had hypertension. Another member also had hypertension, and the erythrocyte count was five million. Engelking[6] described polycythemic traits in three generations of a family; in the last generation, six of 13 children had erythrocyte counts ranging from 8 million to 13.6 million with hemoglobin value between 140 per cent and 185 per cent. In two the spleen was palpably enlarged, and in three there was clubbing of the fingers. Infantilism was coexistent with polycythemia in five of the children. Kretschmer[10] recorded polycythemia in three children in a single family. The father was not examined, but the mother was normal. In two of the three children, the clubbing of the fingers and toes and the cardiac findings led to suspicion that the polycythemia was secondary to congenital heart lesions. In the other instances, no such associated constitutional abnormalities were present. Tancré[16] reported a patient with an erythrocyte count of 14.2 million, hemoglobin value of 17.8 per cent and leukocyte count of 18,300. This patient had a sister with erythrocyte count of 6.1 million but no symptoms. Weil and Stiefel[18] described a patient with erythrocyte count ranging from 5.5 million to 7 million and hemoglobin values from 115 per cent to 130 per cent. Cyanosis of the lips and extremities was noted, and the liver and spleen were palpably enlarged. The patient's brother was cyanotic, and the erythrocyte count was 6.44 million. He had no symptoms, and the liver and spleen were not enlarged.

In addition to a review of the previously reported cases of familial polycythemia, Spodaro and Forkner[15] described a family in which splenomegaly as well as high erythrocyte

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The work herein reported was aided in part by funds provided by Mrs. Edith M. Kiersted.

counts (average 5.98 to 7.8 million) was observed in four members of the ten studied. Another member of the family had an enlarged spleen but normal erythrocyte count, and three other members had elevated erythrocyte counts (average of 5.92 to 6.91 million) but no enlargement of the spleen. The benign course of the disease, absence of leukocytosis, and the normal hemoglobin values and basal metabolic rates in all the patients in the family led Spodaro and Forkner to conclude that the condition differed from polycythemia vera, and they suggested the term "benign familial polycythemia."

In 1939, Nadler and Cohn[14] again reviewed the literature and in addition reported upon a family that they had studied in which four of 11 children had erythrocyte counts from 7.48 million to 8.8 million with hemoglobins from 21 gm. to 24.3 gm. per 100 cc. and packed red cell volume of 61 per cent to 69 per cent of the whole blood. The mother stated that these four children had had "red faces" since birth. There was no evidence of factors which might initiate secondary polycythemia. There was no hypertension, and in only one case was the spleen (barely) palpable. One child had Little's disease. All four children had abnormally high blood volume—from 95 cc. to 133 cc. per kilogram of body weight.

Thus, there seem to be eight authentic examples of familial polycythemia reported in the literature. Other investigators have described conditions which they thought were familial polycythemia, but insufficient evidence is given to establish the disease as familial, or the clinical and hematological data do not definitely point to this diagnosis.

Many instances of leukemia in two or more members of a single family have been reported, and the question of genetic factors has been discussed.[1, 4, 17] Videbaek[17] in 1947 reviewed the 26 reported instances of "apparently incontrovertible" familial leukemia, and added his own report of 13 families, making a total of 39 families in which the disease occurred in two or more members. Certainly it is rarely possible to find familial tendencies when study is made of a large number of patients with leukemia. In the authors' experience during the past 15 years with over 500 patients with leukemia, evidence of leukemia in immediate or distant relatives was found in only three or four families.

A review of the literature revealed four instances of both polycythemia and leukemia in a single family. Guggenheimer[7] reported the case of a patient with polycythemia whose mother died of leukemia. Gutzeit[8] reported a case in which a patient with polycythemia had a son who was treated for a "definite" lymphatic leukemia. In a case of polycythemia reported by Halse,[9] the patient's uncle died of leukemia. Videbaek[17] observed a patient with leukemia whose aunt was under treatment for polycythemia. In addition to the family reported in this presentation, the authors have under observation two other patients with polycythemia vera who have sisters who apparently died of leukemia. Otherwise, in a study of approximately 150 patients with polycythemia vera, there have been no other authentic examples of polycythemia or leukemia in close relatives.

In the family here reported upon, three of the members were referred for treatment of definite blood dyscrasia, and the mother had symptoms strongly suggestive of polycythemia. Other members of the family, unfortunately, were not available for study. Of the three patients studied, one had an established diagnosis of myelogenous leukemia which proved fatal three years later, and two had symptoms and physical and laboratory findings which were typical of polycythemia vera.

CASE REPORTS

CASE 1: A white housewife, aged 57, was well until September 1940, when she became aware of undue fatigue, slight loss of weight, and pain in the left leg at the site of rather large varicose veins. She entered a hospital for vein ligation, and in the course of a complete examination an abnormal blood picture typical of myelogenous leukemia was noted.

Prior to the onset of the symptoms described, the patient had been in excellent health. Five babies were delivered normally, and the children had no known blood abnormalities. In 1933, at the age of 50, menorrhagia developed, but after a uterine curettage a normal menstrual cycle was resumed until at age 52 menorrhagia developed again. Dilatation and curettage then were followed by complete cessation of menses, and the patient semed to be in good health until the onset of symptoms in 1940.

Family history. The mother died at the age of 78 of cardiovascular disease. During the last three years of her life she had had burning pain on the plantar surfaces of the toes with a bluish-red discoloration aggravated by exercise or heat and relieved by exposure to cold. The patient's father died at the age of 91 of causes incidental to age. There were 15 children in all. One brother, aged 67, now dead (see Case 2), had a known diagnosis of polycythemia, and a second brother had cardiovascular disease. A third brother had diabetes, an erythrocyte count of over 6 million, and hypertension which was treated by venesections. Five other brothers are living and well. One sister has known polycythemia. Five other sisters are living and well.

A report of the physical examination of the patient stated that she was observed to be well developed and nourished, appearing to be about the stated age. Slight pallor was noted but the skin was free of rashes. There were small tonsillar tags but no mucous membrane hemorrhages. The pupils reacted normally, and the optic fundi were considered normal. The thyroid gland was small, and the cervical nodes were not enlarged. The heart and lungs were normal to physical examination. The blood pressure was 130 mm. of mercury systolic and 70 mm. diastolic. On abdominal palpation an enlarged spleen could be felt extending 2½ inches below the costal margin on deep inspiration. Axillary and inguinal nodes were small. The extremities were normal except for varicose veins. Results of pelvic and rectal examinations were essentially normal, as were results of neurologic examination. Hematologic studies at the time of the initial examination showed the following: Erythrocytes numbered 4.31 million, with 2.6 per cent reticulocytes; and the hemoglobin content was 12.8 gm. per 100 cc. Leukocytes numbered 65,000 and platelets 2,517,000. The leukocyte differential was 2 per cent basophils, 35 per cent "C" myelocytes, 8 per cent "B" myelocytes, 2 per cent "A" myelocytes, 12 per cent metamyelocytes, 3 per cent band cells, 28 per cent segmented cells, 6 per cent lymphocytes, 4 per cent monocytes, 2 plus anisocytosis, and 1 plus poikilocytosis.

The patient was referred for treatment with radioactive phosphorus, and therapy was initiated in January 1941, at which time the leukocyte count was 130,700. After nine months of moderately intensive therapy, a remission was induced.[11] The patient then remained well clinically and in good hematologic remission until September 1942, when anorexia, nausea and vomiting developed, and subsequently fatigue, neuralgic pains in the legs, night sweats, and loss of weight. The leukocyte count began to rise gradually and immature forms were increasingly evident in spite of continued therapy. The condition of the patient deteriorated steadily, increasing anemia developed and the patient died January 5, 1943.

* * *

CASE 2: A male physician, aged 68 when first observed by the authors, was in good health until 1927, when the patient was 54 years of age. At that time a painful burning sensation in the toes developed, accompanied by bluish-red dis-

colorations and slight swelling. Soon thereafter, the patient noticed hyperesthesia, tenderness, and discoloration of the fingers. These symptoms were decreased in the winter and were considerably aggravated in hot weather. A diagnosis of erythromelalgia was made,[3] and symptomatic relief was obtained with the use of acetylsalicylic acid. In 1934, the diagnosis of polycythemia was made, and therapy during the next four years consisted of phlebotomies at infrequent intervals without striking relief of symptoms. On one occasion pulmonary embolism occurred ten days after venesection. In 1939, phlebotomies were carried out to lower the erythrocyte count to a normal level, and the patient was placed on phenylhydrazine therapy which was continued for three years with slight relief of symptoms.

The patient had had pneumonia and empyema at age 6. Hypertensive vascular disease, pulmonary emphysema, and left renal calculus had been diagnosed before the patient was observed by the authors, and gout had been a complicating factor since 1930.

(The family history was described in Case 1.)

Upon physical examination the patient was observed to be pale and chronically ill. No lesions of the skin or mucous membranes were observed, and there was no lymph node enlargement. The cardiac outline was at the upper limit of normal size with a silhouette sugggestive of left ventricular hypertrophy. The blood pressure was 180 mm. of mercury systolic and 88 mm. diastolic. The heart rhythm was regular, and the rate normal. No murmurs were heard. The lungs were clear to auscultation. The spleen tip was palpable five finger-breadths below the costal margin on the left, and the liver edge extended four finger-breadths below the costal margin on the right. No cyanosis, edema, or clubbing were noted in the examination of the extremities. Hematologic studies revealed the following: Erythrocytes numbered 7.62 million, with hemoglobin 11.7 gm. per 100 cc.; leukocytes numbered 46,000, and platelets 450,000. The packed red cell volume was 40 per cent of the whole blood. The urine contained albumin (4+), four to seven erythrocytes per high-power field, numerous leukocytes, and occasional hyaline casts. The non-protein nitrogen content per 100 cc. was 50 mg., the uric acid content 10 mg. and the oxygen saturation 90 per cent.

Therapy with radioactive phosphorus[12] was begun in June 1942, and 20 millicuries was given over a period of two months. This was followed by definite subjective improvement with a disappearance of symptoms of both erythromelalgia and gout. The spleen decreased almost to normal in size and a progressive fall in the erythrocyte count from 7.62 million to 5.25 million was observed over a period of six months. During this time, the leukocyte count fell from 46,000 to 4,250. Additional P^{32} was given in 1943, 1944, and 1945, and a normal hematologic picture was maintained. During this time the subjective symptoms were minimal as long as the blood picture was kept within normal limits.

In 1945, nephrectomy was done on the left side because of abscess formation secondary to the kidney stone. Convalescence was uneventful, but elevation of the non-protein nitrogen level persisted. The course was gradually but progressively downhill until the patient died in uremia on June 22, 1947, at the age of 74. Necropsy was not done.

* * *

Case 3: The patient, a woman 54 years of age, first noticed dryness and intense itching of the skin in 1924 at the age of 38. In 1934 polycythemia was diagnosed and a correlation was noted between the severity of the pruritus and the number of erythrocytes in the blood. When the erythrocyte count was kept at the level of approximately 5 million by phlebotomies, the symptoms were ameliorated, although not relieved completely. X-ray therapy had never been used. More recently the patient had noticed small scattered purpuric spots over her body. Histamine injections, histaminase tablets, vitamin preparations, potassium chloride, and theelin in oil were tried at various times but did not relieve the symptoms. Previously the patient had been in good health. Thyroidectomy and tonsillectomy were uneventful, and three pregnancies were normal. The children are all well.

(The family history was described in Case 1.)

Upon physical examination, Feb. 11, 1941, rough, scaling, fissured skin lesions of eczematoid type, as well as scattered purpuric lesions, were noted. The tongue was serrated and reddened. The heart was enlarged slightly to the left. The blood pressure was 180 mm. of mercury systolic and 80 mm. diastolic. There was a blowing systolic murmur at the base of the heart. The abdominal musculature was relaxed; the spleen and liver could not be palpated.

Laboratory data, Feb. 11, 1941, were as follows: Erythrocytes numbered 5.01 million; the hemoglobin value was 76 per cent; leukocytes numbered 21,900. Therapy with phlebotomies was withheld and on Sept. 12, 1941, the erythrocyte count was 8.63 million, the hemoglobin value 111 per cent (15.3 gm. per 100 cc.), the platelet count 1,329,000, and the leukocyte count 27,900 with a normal cell differential.

Therapy with radioactive phosphorus[12] was begun with an initial dose of 6.9 millicuries Sept. 15, 1941. The blood cell counts gradually returned to normal and the hematologic remission continued until December 1943, when the cell counts were as follows: Erythrocytes 8.64 million with hemoglobin value of 118 per cent; leukocytes, 13,050. Packed cell volume was 62 per cent of the whole blood. During this time the pruritus had been greatly improved, although it was not completely eliminated. The patient was treated again with P^{32} in 1944 (6 millicuries in January and 7 millicuries in February), and complete hematologic remission was again induced. The itching lessened but was present to an annoying extent for several months before the blood cell counts rose again to polycythemic levels. On June 11, 1946, the results of blood examination were: Erythrocytes, 6.38 million; hemoglobin value 122 per cent (17.7 gm. per 100 cc.); leukocytes, 15,700; packed cell volume 55.8 per cent. At that time the spleen was palpable three finger-breadths below the left costal margin. Examination of sternal marrow revealed hyperplasia of the erythropoietic system with a Myeloid Erythroid ratio of 1.6:1. The oxygen saturation was 97 per cent. After several venesections, the blood cell counts on Oct. 25, 1946, were as follows: Erythrocytes, 7.8 million, with hemoglobin value 86 per cent; leukocytes, 18,550. Administration of 4 millicuries of P^{32} in December 1946 brought about a temporary drop in the blood cell counts, and additional P^{32} (3.2 millicuries) was given in July 1947, followed by a satisfactory remission and great improvement in clinical symptoms.

Comment: The case of myelogenous leukemia described in this instance presented no unusual features. The brother and sister were thought to have true polycythemia, and the absence of intense redness or cyanosis of the skin was attributed to the fact that each patient had been treated previously with phlebotomies and had small hypochromic red cells when first observed by the authors. In each case, the erythrocytosis was associated with leukocytosis and elevated platelet count. The hematocrit values were normal in each instance as a result of previous repeated bleedings, and the reticulocyte counts were never significantly elevated. The spleen was palpably enlarged in each case, but in one case (Case 2) the splenomegaly was a constant feature, whereas in Case 3 the spleen was palpable during active phases of the disease, but was not palpable when the disease was in hematologic remission.

It is unfortunate that all members of the family could not be studied even though they had no symptoms suggestive of blood dyscrasia. Only the mother had a history compatible with the diagnosis of polycythemia, and her symptoms of erythromelalgia were almost identical to those of the second patient in whom a definite relationship existed between these symptoms and the elevated erythrocyte count.

The cases reported herein differ considerably from those of so-called "benign familial polycythemia" described by Spodaro and Forkner[15] in regard to the severity of symptoms necessitating intensive therapy, as well as the presence of other features commonly seen in association with polycythemia vera, namely, the leukocytosis, the high platelet count, and in one instance, gout and erythromelalgia.[3] The occurrence of two cases of polycythemia vera and one case of leukemia in a single family is of particular interest in the light of the high incidence of leukemia occurring as a complication of polycythemia rubra vera[12, 13] and because so few reports of the occurrence of both polycythemia and leukemia in a single family were found in the literature.

SUMMARY

There are eight authentic examples of familial polycythemia and 39 instances of familial leukemia reported in the literature, but the authors found only four instances of the occurrence of both polycythemia and leukemia in the members of one family.

In the family studied by the authors, two cases of polycythemia and one case of myelogenous leukemia in a brother and two sisters are reported. The possible existence of polycythemia in an earlier generation of the family could only be conjectured.

The two patients diagnosed as having polycythemia had typical features of polycythemia vera and responded well to radioactive phosphorus therapy.

The authors wish to thank Dr. J. C. Hayward for providing valuable information concerning the details of the family history of these patients, and Mrs. Nancy R. Durning for her assistance in checking literature and gathering data for this report.

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EDITORIAL

Hospitals — With Whose Money?

The Council of the California Medical Association has devoted much time in recent years to discussions of the pros and cons of building hospital facilities with public or with private funds. On two occasions the Council has directed the attention of the county medical societies to some of the cautions which should be observed before local societies or physicians succumb to the lure of "free money" for hospital construction.

Gist of the Council's twice-repeated suggestions has been that public funds for hospital construction should be used only as a last resort after all sources of private funds have been investigated and found unavailable.

Confirmation of the Council's attitude has just been furnished in a progress report of the Association's Committee on Rural Medical Service, which has been looking things over, including rural hospitals, in several areas of California. Without entering into the political or professional staff membership aspects of hospitals built wholly or partially with public money, the committee has uncovered some startling physical features in at least two such institutions.

One hospital recently completed a 28-bed addition of general beds and a maternity unit. Included in the maternity section is a completely-equipped obstetrical surgery, costing about $25,000, which is to be used only for obstetrical cases. Designed to eliminate contamination, such a surgery might be an understandable feature of a large hospital. However, on the basis of about 250 deliveries per year in this hospital, and allowing for about five per cent cesarean deliveries, this costly feature will be used only a few times each year. Of course, it will be available for circumcisions, which are not generally considered as requiring special facilities, even in large hospitals.

In another hospital, built with governmental funds, a 32-bed institution has been completely equipped with a modern laundry, which to date has not been used. If the unit were put into operation, the salaries of the operating personnel would cost two and one-half to three times the present laundry bill, using outside service. Here it is obvious that the taxpayers' money will lie dormant for an indefinite period, especially with the hospital census running 50 to 60 per cent.

In contrast to these two hospitals, the committee has surveyed a 25-bed hospital which was built entirely from private funds and used public money only in a small amount for equipment. In this instance a workable, although somewhat unusual, plant design has kept the hospital cost to a minimum and has permitted a highly successful and satisfactory operation for more than a year.

The committee's report summarizes the rural hospital construction situation by suggesting that local conditions and requirements should be the principal guides in building rural hospitals and that professional help in architecture, equipment and planning be called upon as supplementary aids only where local resources are not available. The report also suggests that governmental requirements in planning and construction may account for at least a part of the inefficient features or facilities of some of the hospitals built in whole or in part with public funds.

The Council's suggestion to "Stop — Look — Listen" may well be reiterated.

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NOTICES AND REPORTS

Council Meeting Minutes

Tentative Draft: Minutes of the 375th Meeting of the Council, Los Angeles, September 9, 1950.

The meeting was called to order by Chairman Shipman in the Biltmore Hotel, Los Angeles, at 9:30 a.m., Saturday, September 9, 1950.

Roll Call:

Present were President Cass, President-elect MacLean, Speaker Alesen, Vice-Speaker Charnock, Councilors Ball, Crane, Dau, Ray, Montgomery, Lum, Pollock, Green, West, Thompson and Shipman and Secretary Daniels. Absent for cause, Councilors Heron, Henderson and Frees, Editor Wilbur.

A quorum present and acting.

Present by invitation during all or part of the meeting were Executive Secretary Hunton, Assistant Executive Secretary Wheeler, Field Secretary Clancy, Legal Counsel Hassard, Messrs. Clem Whitaker, Jr., James Dorais and Ned Burman of public relations counsel, Mr. Ben H. Read of the Public Health League of California, county society executive secretaries Wood of San Mateo, Donovan of Santa Clara, Cochems of Los Angeles, Young of San Diego, Tobitt of Orange, Waterson of Alameda, Gillette of Fresno and Venables of Kern; Malcolm Merrill of the State Department of Public Health; Lester Lawrence, secretary of the Alameda County Medical Association; Thomas F. O'Connell of the San Diego Blood Bank, and Drs. John Ruddock, John R. Upton, C. A. Broaddus, Francis J. Cox, Justin J. Stein and Christopher Leggo, appearing in behalf of standing or special committees of the Association or the Council, as listed in these minutes.

1. *Minutes for Approval:*

(a) On motion duly made and seconded, minutes of the 374th Council meeting, held May 27, 1950, were approved.

(b) On motion duly made and seconded, minutes of the 222nd Executive Committee meeting, held June 15, 1950, were approved.

(c) On motion duly made and seconded, minutes of the 223rd Executive Committee meeting, held August 10, 1950, were approved.

2. *Membership:*

(a) A report of membership as of September 1, 1950, was received.

(b) On motion duly made and seconded, five members whose 1949 dues had been received since May 27, 1950, were reinstated to membership.

(c) On motion duly made and seconded in each instance, five applicants were elected to Associate Membership. These were: James T. Duncan and James C. Malcolm, Alameda County; Marshall J. Fiese, Fresno County; Manuel Kalman, Marin County; Erwin P. Brauner, Orange County.

(d) On motion duly made and seconded, Walter Christiansen of Los Angeles County was elected to Life Membership.

(e) On motion duly made and seconded in each instance, four applicants were elected to Retired Membership. These were: A. Russell Moodie, Kern County; Morris W. Haworth, Sacramento County; Wm. Palmer Lucas, San Francisco County; Clarence Tyley Roome, Santa Barbara County.

(f) On motion duly made and seconded in each instance, reductions in dues were granted to seven applicants because of illness or postgraduate studies.

3. *Blood Bank Commission:*

John R. Upton, chairman of the Blood Bank Commission, reported on the status of the statewide plan of blood banks, stating that seven banks are now in operation, two others about to start and several others in various stages of planning. He also reported that a reciprocity agreement had been reached between the commission and the American Red Cross, to permit the exchange of blood on mutually acceptable terms between community and Red Cross blood banks.

Francis E. West reported on the San Diego Blood Bank, which has been incorporated to take over the operations of the former blood bank maintained under the auspices of the county medical society, the city-county government, the Navy and the Red Cross. He reported that for the first year of operation the new blood bank estimated a total cost of $71,480, exclusive of cash receipts. He stated that

the San Diego County Medical Society could advance $10,000 toward this total cost and that a loan of $10,000 additional would be made by the Doctors Business Bureau in that county.

John W. Green, a member of the A.M.A. Blood Bank Commission, reported on a recent Washington meeting between the A.M.A. commission, the American Red Cross and several government agencies. He also presented a resolution for Council consideration (see below).

Dr. Upton requested the advance of $3,500 to cover the cost of bottles and tubing for blood banks in Sonoma and Eureka ($750 each) and San Diego ($2,000), to provide a three-month supply. On motion duly made and seconded, this advance was voted.

On motion duly made and seconded, Dr. Green's resolution was adopted. This reads as follows:

WHEREAS, The California Medical Association through its Blood Bank Commission has evidenced its wish to furnish adequate blood to our citizens when needed at an economical, non-profit level, and

WHEREAS, A reciprocal agreement with the Pacific Area Office of the American Red Cross is now under consideration to enhance the effectiveness of the mutual high purposes of this commission and the American Red Cross, and

WHEREAS, The local county medical societies are considered the best judges of what will best serve their communities in this regard, by both the California Medical Association and the American Red Cross, and

WHEREAS, The recent decision of the San Diego County Medical Society to authorize a community non-profit blood bank under the auspices of the Blood Bank Commission of the California Medical Association for their area has apparently not been accepted as final by either the Pacific Area Office or the San Diego chapter of the American Red Cross, now, be it here

Resolved: That the Pacific Area Office of the American Red Cross be requested to reaffirm the policy of the National American Red Cross in 1948 with the American Medical Association regarding local county medical society decisions as to their blood bank facilities and to so communicate this reaffirmation to the San Diego Chapter of the American Red Cross, and, be it further

Resolved: That such reaffirmation will be regarded by the California Medical Association as an indication of the efficiency and good faith to be expected in the Reciprocity Agreement now under consideration and that voluntary aid from the San Diego chapter of the American Red Cross will, if needed, be authorized for the benefit of the San Diego Blood Bank program under the terms of the proposed reciprocal agreement when mutually ratified.

On motion duly made and seconded, and amended to increase the amount from $30,000 to $50,000, the Council voted to lend $50,000 to the San Diego Blood Bank, without interest, to assist it in starting its program. This loan supersedes the previous authorization of $12,000. Terms of repayment are to be arranged by the Executive Committee and legal counsel, in accordance with the Council resolution of May 27, 1950.

At this point Dr. Albert C. Daniels was introduced by the chairman as the new Secretary-Treasurer of the Association, appointed by the Executive Committee and confirmed by vote of the Council.

4. *Committee on Industrial Accident Commission:*

Dr. Francis J. Cox, chairman of the Committee on Industrial Accident Commission, reported on the meeting held between his committee and the negotiating committee of compensation insurance carriers. The Council thanked Dr. Cox for his report and requested that he prepare a summary of it for publication in the official journal.

5. *State Department of Public Health:*

Dr. Malcolm Merrill reported to the Council on (1) the activation of the Crippled Children's Advisory Committee, which has now met, (2) the meeting of the committee on the proposed Morbidity Study, and (3) the agreement to have medical representation on the State Disaster Council.

6. *Committee on Industrial Health:*

Dr. Christopher Leggo, chairman of the Committee on Industrial Health, presented a proposed statement of principles for the guidance of industrial nurses and their employers. After discussion, it was moved, seconded and voted to table action on this statement pending further clarification of the principles involved by the committee.

7. *Advisory Planning Committee:*

Mr. Hunton, chairman, reported that the Advisory Planning Committee had met the preceding day. The committee had adopted a resolution calling for scientific approach to the problem of individual physician-patient relationships, on which future reports would be made.

8. *Committee on Associated Societies and Technical Groups:*

A report of the committee on Resolution No. 19 of the 1950 House of Delegates was read. The report recommended that psychologists, through their professional society, prepare a list of qualified psychologists to work under the direction of physicians, that such list be made available to physicians but not to the public, and that such list be subjected to critical review at annual intervals. On motion duly made and seconded, the report of the committee was approved.

9. *Committee on Hospitals, Dispensaries and Clinics:*

On motion duly made and seconded, it was voted to accept, with regret, the resignation of Dr. John C. Sharp as a member and chairman of the Committee on Hospitals, Dispensaries and Clinics. It was regularly moved, seconded and voted to appoint Dr.

Howard Miles of Salinas as a member of the committee to succeed Dr. Sharp and to name Dr. Francis E. Jacobs of San Diego as chairman.

10. *Committee on Public Health and Public Agencies:*

Dr. Thompson, at the request of Dr. Alesen, chairman, discussed the use of public funds for hospital construction. Dr. West reported that an early meeting had been arranged for the consideration of the question of physicians accepting fees for care of patients whose expenses were being borne by national organizations which rely on public financial support.

11. *Committee on C.P.S. Administrative Matters:*

A report from the Committee on C.P.S. Administrative Matters was read and discussed. The report urged creation of a committee of C.M.A. officers (President as chairman, President-elect, speaker, Council chairman, legislative chairman) to serve as a liaison committee, together with the President of the C.P.S. trustees and two members to be elected by the House of Delegates, with C.P.S. trustees in an advisory body on matters of policy or economic import. On motion duly made and seconded, the report was approved.

12. *Committee on Emergency Medical Service:*

Dr. Justin J. Stein, chairman of the Committee on Emergency Medical Service, reported on the activities of the committee and stated that he had been appointed chairman of a state advisory committee to the State Disaster Council and had attended several meetings of that body. Dr. Stein was praised by the chairman for the work of his committee.

13. *Committee on Postgraduate Activities:*

Dr. John Ruddock, chairman of the Committee on Postgraduate Activities, reported that five two-day institutes were planned for the fall and winter season, together with numerous one-day conferences in other locations. For the two-day institutes he requested authority to establish a registration fee of $5 as a means of increasing interest in the institutes. On motion duly made and seconded, this recommendation was approved.

14. *Cancer Commission:*

(a) On motion duly made and seconded, it was voted to approve the employment by the Cancer Commission of Dr. Franklin C. Hill as medical director.

(b) On motion duly made and seconded, it was voted to approve the purchase by the State Department of Public Health of films produced by the American Cancer Society on self-examination of the breast, these films to be used for lay education and to be handled by the California Division of the American Cancer Society in accordance with terms agreed upon by the Cancer Commission.

15. *Hospital Staff Meetings:*

A letter from the Alameda County Medical Association, relative to compulsory attendance at hospital staff meetings, was read and discussed. On motion duly made and seconded, it was voted to refer the matter to the Committee on Associated Societies and Technical Groups.

16. *California Physicians' Service:*

Dr. Kendrick Smith, representing the C.P.S. Trustees, reported to the Council on the financial position of C.P.S. He stated that the only contract which is not now paying its own way is the two-visit deductible medical rider and that steps are being taken to revise this contract to make it self-supporting. Dr. Cass requested that the delegates to the A.M.A. be instructed to introduce a resolution asking the Council on Medical Service of the A.M.A. to restate its position in approving medically-sponsored prepayment plans. On motion duly made and seconded, it was voted to instruct the A.M.A. delegates accordingly.

17. *Interim Session of House of Delegates:*

Discussion was held as to the subjects to be included in the call of the interim session of the House of Delegates scheduled for December 2 and 3, 1950. After considerable discussion it was regularly moved, seconded and voted that this session not be held, on account of the evident lack of suitable subjects to warrant its convention.

18. *Public Policy and Legislation:*

Dr. D. H. Murray, chairman of the Committee on Public Policy and Legislation, and Mr. Ben H. Read, executive secretary of the Public Health League of California, discussed the legislative situation, both state and national, and reported that a meeting had been scheduled with representatives of allied professional groups for the discussion of matterms of mutual interest.

19. *Student Nurse Recruitment:*

A request for a contribution to a fund to finance a campaign of student nurse recruitment was read, the request showing that some $4,660 had been contributed by other organizations, including the Association of California Hospitals and several nursing groups and hospitals. On motion duly made and seconded, it was voted to appropriate $1,250 to this fund.

20. *Legal Department:*

Mr. Hassard reported on several court decisions of interest to the Association.

21. *Alameda-Contra Costa Medical Association:*

Dr. Lum reported that the approval of the proposed by-laws by the members of the Contra Costa County Medical Society was the only necessary step in compliance with the authorization of the 1950 House of Delegates for issuance of a charter to the Alameda-Contra Costa Medical Association. It was regularly moved, seconded and voted that when this approval is secured and the charters of the two existing societies are surrendered, if possible, the secretary be instructed to issue a new charter to the combined society.

22. *World Federalism:*

On motion duly made and seconded, the following resolution was unanimously adopted:

WHEREAS, The California Medical Association has vigorously and successfully opposed recurring attempts to introduce socialized systems of medical care in California for many years, and

WHEREAS, The doctors of California have wholeheartedly supported the work of the American Medical Association in combating the politically inspired threat of socialized medicine on a national scale, and

WHEREAS, American health and medical standards, achieved under the American free enterprise system, are vastly superior to those of the world's other civilized countries, in most of which the private practice of medicine has been virtually eliminated by socialistic governments; now therefore, be it

Resolved: That the California Medical Association record its opposition to the concept of world government under which the American system of free enterprise would be endangered by the majority rule of conflicting systems, and reject any and all current attempts to that end as premature and inconsistent with the forthright stand of California doctors of medicine against the socialization of medicine in America.

23. *Time and Place of Next Meeting:*

It was regularly moved, seconded and voted that the next meeting of the Council would be at the direction of the Executive Committee.

Adjournment:

There being no further business to come before the meeting, it was adjourned at 6:00 p.m.

SIDNEY J. SHIPMAN, M.D., *Chairman*
ALBERT C. DANIELS, M.D., *Secretary*

Executive Committee Minutes

Tentative Draft: Minutes of the 223rd Meeting of the Executive Committee, San Francisco, August 10, 1950.

The meeting was called to order by Chairman Lum in Room 218 of the St. Francis Hotel, San Francisco, at 3:00 p.m., Thursday, August 10, 1950.

Roll Call:

Present were President Cass, President-elect MacLean, Council Chairman Shipman, Speaker Alesen and Auditing Committee Chairman Lum; Assistant Secretary-Treasurer Montgomery. Present by invitation were Executive Secretary Hunton, Assistant Executive Secretary Wheeler, Legal Counsel Hassard, Mr. Ben Read, executive secretary of the Public Health League of California, and Dr. Albert C. Daniels, committee nominee for the office of Secretary-Treasurer.

1. *Financial:*

(a) It was regularly moved, seconded and voted to appropriate $2,500 to meet the expenses of the Interim Session of the House of Delegates, to be held December 2 and 3, 1950, in Sacramento.

(b) It was regularly moved, seconded and voted that the constitutional provisions regarding waiver of dues of members in military service be considered effective and to recommend to the Council, for its recommendation to the House of Delegates, the pro rata refund of 1950 dues to members called into service during the year.

It was regularly moved, seconded and voted that the county medical societies be informed of these steps and of the progress of plans for the recruitment of medical officers for the armed forces to date.

In response to a request from the Council on Emergency Medical Service of the American Medical Association, it was regularly moved, seconded and voted to make nominations for selection of a state chairman for a proposed procurement and assignment service. Several suggestions for such nominees were considered.

It was agreed that the county medical societies should be advised of current developments in regard to medical officer requirements for the armed forces.

(c) On motion duly made and seconded, it was voted to renew the subscription of $1,000 annually to the California State Chamber of Commerce.

2. *Committee on Emergency Medical Service:*

The committee reviewed the report of the Committee on Emergency Medical Service. It was regularly moved, seconded and voted that reprints of an article to appear in the *Bulletin of the Los Angeles County Medical Association* be purchased for distribution to members outside that area.

It was regularly moved, seconded and voted that the committee be authorized to purchase office equipment up to a value of $200.

It was the sense of the Executive Committee that the military and civilian aspects of emergency medical service be clearly separated.

3. *Committee on Advertising:*

(a) On motion duly made and seconded, it was voted to accept with regret the resignation of Dr. C. L. Cooley as a member of the Committee on Advertising and to name Dr. W. Dayton Clark to succeed to this appointment.

(b) On the matter of the use of physicians' names in the advertising of hospitals and sanatoria, it was regularly moved, seconded and voted to refer the question to the Committee on Hospitals, Dis-

pensaries and Clinics for study and an expression of opinion to the Council.

4. *Legal Department:*

(a) Mr. Hassard reported on certain activities of so-called health organizations and on motion duly made and seconded, it was voted to authorize him to proceed with the investigation of such groups.

(b) Mr. Hassard discussed several current court cases of interest to the Association and in one case concerning the question of expert testimony without the consent of the witness, it was regularly moved, seconded and voted to authorize him to appear on behalf of the Superior Court of San Francisco County.

(c) It was regularly moved, seconded and voted that Dr. Donald Cass be authorized to appear before an interim committee of the Legislature on August 28, to present a statement relative to nursing and that a pilot survey to determine the needs for nursing services throughout the state be taken for presentation to this committee at a later public hearing.

5. *Appointment of Secretary-Treasurer:*

The Executive Secretary reported on the returns from Councilors on an informal poll taken on the nomination of Dr. Albert C. Daniels for appointment as Secretary-Treasurer of the Association. It was agreed that the unanimous agreement of a quorum of the Council on this nomination should be considered as official approval and that the office be authorized to proceed on that basis.

6. *Time and Place of Next Council Meeting:*

It was agreed that the next meeting of the Council would be called for Saturday, September 9, at the Biltmore Hotel, Los Angeles.

Adjournment.

DONALD D. LUM, M.D., *Chairman*
M. LAURENCE MONTGOMERY, M.D.,
Assistant Secretary-Treasurer

C. M. A. Postgraduate Institutes

The California Medical Association through its Committee on Postgraduate Activities consisting of Dr. John C. Ruddock of Los Angeles, chairman, Dr. Carroll Andrews of Sonoma, Dr. Edward C. Rosenow, Jr., of Los Angeles, and (ex-officio) Dr. Albert C. Daniels of San Francisco, secretary of the C.M.A., is planning a new departure in carrying postgraduate instruction to physicians of the non-metropolitan areas of California. Dr. A. C. Broaddus of Stockton is the Director of Postgraduate Activities, appointed by the Association to formulate and carry out, as authorized by the committee, plans for more extensive postgraduate opportunities for all California physicians.

Each year postgraduate institutes are to be held in five or more widely separated regional centers where such opportunities are not at present available. The program for each institute will be arranged by a committee of the local medical society working with the director of the postgraduate department of one of the medical schools of Los Angeles or San Francisco. A registration fee of $5 will be charged entitling the registrant to attend one or all of the institutes of the season. Funds so collected will be used to bring in outstanding speakers from eastern centers as well as from medical schools in California.

The Santa Barbara Medical and Surgical Institute will meet October 12 and 13 in Santa Barbara at the Bissell Auditorium of the Cottage Hospital. (The program prepared by the local committee, Dr. H. V. Findlay, chairman, and Dr. H. M. Walton, chairman of the postgraduate extension work of the College of Medical Evangelists, is presented in detail under "News and Notes" of this issue.)

The Fresno Medical and Surgical Institute will be held on Thursday and Friday, November 2 and 3, at the Hotel Californian in Fresno. (This program is also shown in detail under "News and Notes" of this issue.) It was prepared by the local committee, Dr. C. S. Mitchell, chairman, cooperating with Dr. S. J. Weinberg of the University of California at Los Angeles.

Three other institutes are in preparation. The Riverside Medical and Surgical Institute will convene January 25 and 26 at the Mission Inn in Riverside. The program is being prepared by the local committee, Dr. Franklin B. Mead, chairman, working with Dr. Edward C. Rosenow, Jr., director, and Dr. Gordon E. Goodhart, associate director, of the Graduate Extension Division of the University of Southern California School of Medicine.

The Sacramento Society for Medical Improvement has named Dr. Herbert W. Jenkins chairman of a committee which is planning the Sacramento Medical and Surgical Institute with Dr. William Northway, assistant dean of the School of Medicine of Stanford University. This will be given February 8 and 9, 1951, in Sacramento.

The last program, the Santa Rosa Institute prepared by Dr. Stacey R. Mettier, director of the postgraduate department of the Medical School of the University of California in accordance with the wishes of Dr. William E. Rogers and his committee of the Sonoma County Medical Society, will be given March 8 and 9, 1951, in Santa Rosa.

All these institutes are open to any regular physician or surgeon of California who registers for any one of them. Plans are being made to get these institutes accepted for full university credit toward the requirements of the Academy of General Practice.

Questions and Answers about C. P. S.

Billing C.P.S. Is Simple

(Editor's Note: To answer questions about C.P.S. billing, this section is entirely devoted to the subject this month.)

Herewith is a reproduction of the C.P.S. Billing Form No. 9, the only form required to file a claim for services rendered by physician-members to a C.P.S. patient. Following are step-by-step instructions for completing the form. Printing or typing should be used for all answers.

PART I: At the time of the first visit, have the patient complete this section of the billing form—giving full name (as it appears on his C.P.S. membership card) and home address.

When the patient's income status is not known, have him check in the appropriate box whether his *gross family income* for the preceding year was over or under $3,600. The C.P.S. income provision is fully expained on the reverse of the last (pink) carbon.

If income is over $3,600, the doctor is entitled to charge the difference between the C.P.S. fee and his usual fee. Any such charges should be discussed *in advance* of rendering services in order to avoid the possibility of later misunderstanding.

If this income is under $3,600 the patient may not be charged in addition to the fee paid by C.P.S. to the physician-member—except for such services as are not covered by the patient's contract.

Space is provided for the patient's signature.

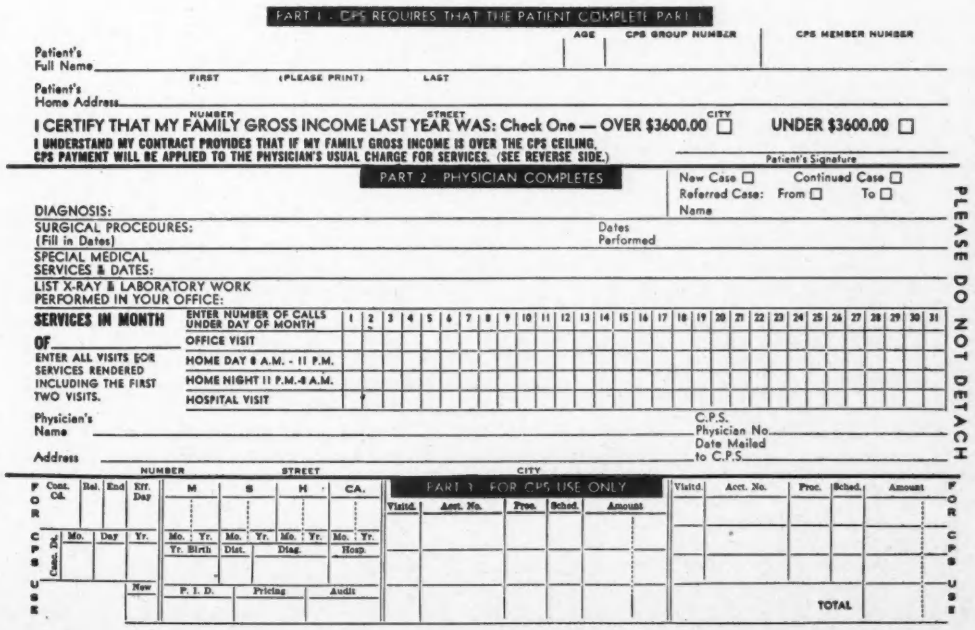
PART II: On *line one* give the diagnosis. At the end of the line indicate if the case is "new" or "continued" and if the patient is referred to or from another doctor. If a referred patient, give the other doctor's name.

On *line two* describe the surgical procedures performed, and give the dates.

On *line three* describe any special medical services rendered, other than those covered by fee for routine office, home or hospital visit. Give dates.

On *line four* list x-ray and laboratory work performed in your office.

Next indicate the month during which services were rendered. Bill C.P.S. once a month for all services rendered that month. Use a separate billing form for each C.P.S. patient, even if members of the same family. If services were rendered in more than one month, use a separate billing form for the services in each month.



PART I - CPS REQUIRES THAT THE PATIENT COMPLETE PART I

Patient's Full Name _____ (PLEASE PRINT) AGE CPS GROUP NUMBER CPS MEMBER NUMBER
FIRST LAST

Patient's Home Address _____
NUMBER STREET CITY

I CERTIFY THAT MY FAMILY GROSS INCOME LAST YEAR WAS: Check One — OVER $3600.00 ☐ UNDER $3600.00 ☐

I UNDERSTAND MY CONTRACT PROVIDES THAT IF MY FAMILY GROSS INCOME IS OVER THE CPS CEILING, CPS PAYMENT WILL BE APPLIED TO THE PHYSICIAN'S USUAL CHARGE FOR SERVICES. (SEE REVERSE SIDE.)

Patient's Signature

PART 2 - PHYSICIAN COMPLETES

New Case ☐ Continued Case ☐
Referred Case: From ☐ To ☐
Name

DIAGNOSIS:
SURGICAL PROCEDURES: (Fill in Dates) Dates Performed
SPECIAL MEDICAL SERVICES & DATES:
LIST X-RAY & LABORATORY WORK PERFORMED IN YOUR OFFICE:

SERVICES IN MONTH OF _____
ENTER ALL VISITS FOR SERVICES RENDERED INCLUDING THE FIRST TWO VISITS.

ENTER NUMBER OF CALLS UNDER DAY OF MONTH	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	31
OFFICE VISIT																															
HOME DAY 8 A.M. - 11 P.M.																															
HOME NIGHT 11 P.M.-8 A.M.																															
HOSPITAL VISIT																															

Physician's Name _____ C.P.S. Physician No. _____
Date Mailed to C.P.S. _____
Address _____
NUMBER STREET CITY

FOR CPS USE ONLY

Cont. Ck.	Bal.	End	Ref. Day	M	S	H	CA.	Visitd.	Acct. No.	Proc.	Sched.	Amount

Case Ref.	Mo.	Day	Yr.	Mo. : Yr. Yr. Birth	Mo. : Yr. Dist.	Mo. : Yr. Diag.	Mo. : Yr. Hosp.

Case Use	New	F. I. D.	Pricing	Audit

Visitd.	Acct. No.	Proc.	Sched.	Amount
			TOTAL	

FOR CPS USE ONLY

ATTENTION PHYSICIAN'S OFFICE: Please do not detach this stub. Detach the pink copy and one carbon. Send CPS the balance of the forms with carbon inserts intact.

PLEASE DO NOT DETACH

Next indicate, in the space provided, all office, hospital, home (day) and home (night) visits during the month. If more than one visit occurred on a certain day, the number of visits should be shown in the column for that day. List *all* visits, including the first two.

The last two lines are for the physician's name, his C.P.S. physician number, his office address, and the date the billing form is mailed to C.P.S.

PART III: This is for C.P.S. use only and requires no action by physicians, their secretaries, or patients.

Each billing form is in quadruplicate. The top *three* copies must be returned to C.P.S. intact (including carbon paper sheets and the right-hand binding). Doctors' offices retain only the pink copy, as indicated on the right-hand binding. Bills must be received by C.P.S. within six months of the month of service to be payable.

If the above step-by-step procedures are followed, clerical work in doctors' offices will be simplified and processing of bills by C.P.S. will be expedited. Moreover, patients will understand any direct charges which doctors may have arranged to make when the income is over $3,600.

NEWS and NOTES

NATIONAL • STATE • COUNTY

ALAMEDA

Officers of the **Pacific Dermatologic Association** for 1951, elected at the recent annual meeting in Oakland, are: President, Dr. Joseph Shaw of Seattle; vice-president, Dr. Hiram Newton of San Diego; secretary-treasurer, Dr. Ervin Epstein of Oakland. The meeting was attended by 125 members.

FRESNO

The first annual session of the **Fresno Medical and Surgical Institute,** arranged through the California Medical Association Committee on Postgraduate Activities, will be held Thursday and Friday, November 2 and 3, 1950, at the Hotel Californian, Fresno. The Institute is sponsored by the Fresno County Medical Society and the teaching staff will be furnished by the School of Medicine and Medical Extension, University of California at Los Angeles, through arrangement with Dr. S. J. Weinberg, Head of Postgraduate Instruction, Medical Extension.

Inquiries and communications regarding the Institute may be addressed to Glenn W. Gillette, 920 Helm Building, Fresno.

Thursday, November 2, 1950

8:00-9:00 a.m.—Registration: Mezzanine Floor, Hotel Californian. (Registration fee $5.00 entitles registrant to attend any or all of the other Postgraduate Institutes in this series 1950-51.)

MORNING SESSION

Chairman: DR. C. S. MITCHELL

9:00-10:00 a.m.—"Diagnosis and Treatment of Virus and Rickettsial Diseases," Dr. Edwin Lennette, Chief of Virus and Rickettsial Laboratories, State Department of Public Health, Berkeley.

10:00-10:30 a.m.—Discussion period.

10:30-11:30 a.m.—"Viral and Rickettsial Diseases," Charles M. Carpenter, M.D., Professor of Infectious Diseases, School of Medicine, University of California, Los Angeles.

11:30-12:00 Noon—Discussion period.

12:00-1:45 p.m.—Luncheon and Round Table: Room 212, Californian Hotel. Chairman, Dr. R. A. Donald.

AFTERNOON SESSION

Chairman: DR. T. A. COLLINS

2:00-3:00 p.m.—"Placentia Previa—Diagnosis and Treatment, with Special Reference to Placentography," Daniel G. Morton, M.D., Professor of Obstetrics and Gynecology, School of Medicine, University of California at Los Angeles.

3:00-3:30 p.m.—Discussion period.

3:30-4:30 p.m.—"Use of Scintillation Counter in Thyroid Uptakes," Raymond L. Libby, Ph.D., Associate Clinical Professor of Radiology, School of Medicine, University of California at Los Angeles.

4:30-5:00 p.m.—Discussion period.

Friday, November 3, 1950

Sessions at the Fresno County Hospital, 4461 Ventura, between Barton and 12th Streets.

9:00-9:30 a.m.—Surgical Case Presentation.

Chairman: DR. C. A. CABELL

9:30-10:30 a.m.—"Chest Surgery, Including Surgical Treatment of Mitral Stenosis," William H. Muller, Jr., M.D., Assistant Professor of Surgery, School of Medicine, University of California at Los Angeles.

10:30-11:00 a.m.—Medical Case Presentations.

Chairman: DR. JOS. BOLKOVATZ

11:00-12 Noon—"The Hemorrhagic Diseases," William N. Valentine, M.D., Assistant Professor of Medicine, School of Medicine, University of California at Los Angeles.

12:15-2:00 p.m.—Luncheon and Round Table: Room 212, Hotel Californian. Chairman, Dr. George Olson. Subject: "Set-up for Atomic Defense Medical Program."

2:00-3:00 p.m.—Chairman: Dr. F. R. Freeto. "The Use of ACTH and Cortisone in Malignant Disease," William S. Adams, M.D., Assistant Professor of Medicine, School of Medicine, University of California at Los Angeles.

3:00-3:30 p.m.—Questions.

3:30-4:30 p.m.—"Respiratory Tract Infections in Children," John M. Adams, M.D., Professor and Chairman of Pediatrics Department, University of California at Los Angeles, School of Medicine.

LOS ANGELES

Dr. Russell Starr of Los Angeles was elected president of the **Western Association of Railroad Surgeons** at the annual convention of that organization in Reno last month. Dr. Douglas L. Gannette of Los Angeles was elected first vice-president, Dr. Harry O. Hurd of San Rafael, treasurer, and Dr. W. W. Cummins of San Francisco, secretary.

* * *

The **Twentieth Annual Postgraduate Symposium of the Los Angeles Heart Association** will be held in the Wilshire-Ebell Theater, Wednesday and Thursday, October 18 and 19. The program follows:

Wednesday Morning, October 18, 1950

9:00—Registration.

9:25—Opening remarks. Lewis T. Bullock, M.D., president, Los Angeles Heart Association.

9:30—Electrokymographic Studies in Valvular Heart Disease and Ventricular Hypertrophy, Edward Phillips, M.D.

9:40—Anticoagulants in Congestive Heart Failure, David C. Levinson, M.D., and George Griffith, M.D., U.S.C. School of Medicine Division of Cardiology, Los Angeles County Hospital.

9:50—Problems Relating to the Employment of Individuals with Heart Disease, Eugene Levine, M.D.

10:00—Indications for and the Results of Resection of Aortic Coarctation, John Jones, M.D.

10:15—Recess.

10:30—What the Los Angeles Heart Association Means to the Doctor, Mr. Jack Spear, executive secretary, Los Angeles Heart Association.

10:45—Blood Volume Studies in Shock Following Myocardial Infarction, Clarence M. Agress, M.D., Marvin Rosenburg, M.D., Abraham Schneiderman, M.D., and E. J. Brotman, M.D., Department of Medicine, Wadsworth General Hospital, Sawtelle.

11:00—Basic Hemodynamic Principles in the Interpretation of Cardiac Disorders, Carl J. Wiggers, M.D., professor of physiology, Western Reserve University.

Wednesday Afternoon

2:00—The Present Status of the Problem of Essential Hypertension, George W. Pickering, M.D., professor of medicine, St. Mary's Hospital, London.

2:45—The Experimental Production and the Mechanism of Auricular Tachycardia and Premature Auricular Systoles in the Human, Eliot Corday, M.D., Alfred Goldman, M.D., Robert Oblath, M.D., Eleanor Gerlach, and Myron Prinzmetal, M.D., Institute for Medical Research, Cedars of Lebanon Hospital.

3:00—The Action of Procaine Amide in Cardiac Arrhythmias, M. H. Nathanson, M.D., and Harold Miller, M.D., U.S.C. Department of Medicine, Division of Cardiology; Department of Medicine, Cedars of Lebanon Hospital.

3:15—Recess.

3:30—Serum Electrolytes and the Electrocardiogram, Telfer Reynolds, M.D., U.S.C. School of Medicine and Los Angeles County Hospital.

3:45—Electrocardiographic Diagnosis of Myocardial Infarction in the Presence of Bundle Branch Block, Morley J. Kert, M.D., Department of Medicine, Wadsworth General Hospital, Sawtelle.

3:55—Resection of the Auricular Appendage, John M. Beal, M.D., William P. Longmire, Jr., M.D., and William H. Leake, M.D., Department of Surgery, Wadsworth General Hospital, Sawtelle.

6:00—Cocktails.

7:15—Dinner Meeting, the California Club, 538 South Flower Street. Guest Speaker: George W. Pickering, M.D.

Thursday Morning, October 19, 1950

9:00—Indications, Limitations and Contraindications of Cardiac Catheterization, Sidney S. Sobin, M.D., Cardiovascular Research Department, Children's Hospital, Los Angeles.

9:15—Factors Affecting the Circulation Time, Morton Lee Pearce, M.D., and Alvin Lewis, M.D., Departments of Medicine and Pathology, U.C.L.A. School of Medicine.

9:25—Pharmacology of Mercurial Diuretics, Adrian Goodman, M.D., U.S.C. Department of Medicine, Division of Cardiology, Los Angeles County Hospital.

9:35—The Toxicity of Mercurial Compounds—Pathological Studies, Edward M. Butt, M.D., chief pathologist, Los Angeles County Hospital.

9:45—Low Serum Sodium Levels in Cardiac Decompensation, Robert F. Maronde, M.D., U.S.C. School of Medicine.

9:55—Results in the Treatment of Rheumatic Fever with ACTH, George Griffith, M.D., Jack A. Sheinkopf, M.D., and Robert Morrison, M.D., U.S.C. Department of Medicine, Division of Cardiology, Los Angeles County Hospital.

10:15—Recess.

10:30—Classic Descriptions of Angina Pectoris and Coronary Disease, William D. Evans, M.D., Department of Medicine, College of Medical Evangelists.

10:45—The Measurement of Regional Circulation, Hardin B. Jones, Ph.D., Division of Medical Physics, University of California, Berkeley.

11:15—Vascular Spasm, George W. Pickering, M.D., professor of medicine, St. Mary's Hospital, London.

Thursday Afternoon

2:00—The Physiological Basis of Myocardial Failure, Carl J. Wiggers, M.D., professor and director, Department of Physiology, Western Reserve University.

3:00—Recess.

3:15—Blood Lipid Transport and Human Atherosclerosis, John W. Gofman, M.D., Ph.D., associate professor of medical physics, University of California, Berkeley.

4:45—Clinical Pathological Conference, George W. Pickering, M.D., Carl J. Wiggers, M.D., Hugh Edmondson, M.D., and L. J. Tragerman, M.D.

SAN FRANCISCO

Dr. Francis L. Chamberlain has been elected president of the newly organized San Francisco Heart Association, Inc. Other officers are Dr. Lowell A. Rantz, vice-president, Dr. Norman E. Freeman, secretary, John F. Forbes, treasurer, and Dr. Robert L. Smith, chairman of the board of governors.

* * *

Advance registrations are already being received by the San Francisco Heart Association for the twenty-first **Annual Postgraduate Symposium on Heart Disease** to be presented at the St. Francis Hotel October 25, 26, 27, 28. Guest speakers will be George W. Pickering, M.D., professor of medicine, University of London, and Carl J. Wiggers, M.D., professor of physiology, School of Medicine, Western Reserve University, Cleveland.

In addition to the two guest speakers, 43 local physicians will participate in the four-day program.

The courses in electrocardiography which proved so popular last year are being presented again this year. Physicians in military service, residents, interns and students will be admitted without registration fee to the scientific sessions.

The symposium program committee consisted of Dr. Maurice Sokolow, chairman, Dr. Robert H. Alway, Dr. Clayton D. Mote, and Dr. David A. Rytand.

TWENTY-FIRST ANNUAL POSTGRADUATE SYMPOSIUM ON HEART DISEASE

October 25, 26, 27, 28, 1950

Colonial Ballroom, St. Francis Hotel

Wednesday Morning, October 25, 1950

9:15 a.m.-12:15 a.m.

COURSES IN ELECTROCARDIOGRAPHY

ELEMENTARY

Presiding: FRANCIS ROCHEX, M.D.

9:15-10:15—Fundamentals of Unipolar Electrocardiography, Winston Benner, M.D.

10:15-11:15—Ventricular Hypertrophy and Bundle-Branch Block, Herbert C. Moffitt, Jr., M.D.

11:15-12:15—Myocardial Infarction, Robert L. Smith, Jr., M.D.

ADVANCED

Presiding: WILLIAM W. NEWMAN, M.D.

9:15-10:15—Newer Concepts of Unipolar Electrocardiography, John J. Sampson, M.D.

10:15-11:15—The Value of Additional Exploratory Leads in Electrocardiographic Diagnosis, Maurice Sokolow, M.D.

11:15-12:15—Errors in the Diagnosis of Myocardial Infarction, Francis L. Chamberlain, M.D.

Wednesday Afternoon, October 25, 1950

1:15 p.m.-4:50 p.m.

Colonial Ballroom, St. Francis Hotel

SESSION ON HEART DISEASE IN CHILDHOOD

Sponsored by the American Academy of Pediatrics, Northern California

Presiding: ROBERT S. LEET, M.D.

President, Northern California Pediatric Society

1:15-1:40—The Significance of Cyanosis, Arthur Selzer, M.D.

1:40-2:05—The Management of Congestive Failure in Infancy and Childhood, Saul J. Robinson, M.D.

2:05-2:30—Cardiac Catheterization—Indications and Limitations, Herbert N. Hultgren, M.D.

2:30-2:55—The Role of Contrast Substances in the Diagnosis of Congenital Heart Disease, Earl R. Miller, M.D.

2:55-3:20—The Present Status of Surgery in Congenital Cardiovascular Disease, H. Brodie Stephens, M.D.

3:20-3:35—Recess.

3:35-4:00—A Pediatric Approach to the Child with Heart Disease, John A. Anderson, M.D.

4:00-4:25—Recent Advances in the Management of Rheumatic Fever, Harold H. Rosenblum, M.D.

4:25-4:50—Arrhythmias in Childhood, Robert H. Alway, M.D.

Wednesday Evening, October 25, 1950

8:00 p.m.

Colonial Ballroom, St. Francis Hotel

Presiding: STACEY METTIER, M.D.

Basic Hemodynamic Principles in the Interpretation of Circulatory Disorders, Carl J. Wiggers, M.D.

(This session and the Thursday evening session are held in collaboration with the Medical Extension (University Extension), University of California Medical School, as one feature of a postgraduate series of 12 evening lectures in general medicine.)

Thursday Morning, October 26, 1950

9:15 a.m.-12:05 p.m.

Colonial Ballroom, St. Francis Hotel

CLINICAL CARDIAC CONFERENCE

Presiding: CLAYTON D. MOTE, M.D.

9:15-11:00—Presentation of selected cases of cardiovascular problems with discussion of diagnosis and treatment.

Participants: William L. Bender, M.D., Gordon E. Hein, M.D., J. K. Lewis, M.D., George W. Pickering, M.D., Hobart Rogers, M.D., Carl J. Wiggers, M.D.

11:00-11:15—Recess.

11:15-12:05—Physiological Basis of Myocardial Failure, Carl J. Wiggers, M.D.

Thursday Afternoon, October 26, 1950

2:00 p.m.-4:30 p.m.

Presiding: J. K. LEWIS, M.D.

2:00-3:00—Hypertensive Cerebral Attacks, George Pickering, M.D.

3:00-3:20—Management of Cerebral Vascular Accident, Henry Newman, M.D.

3:20-3:40—Clinical Use of Derivatives of Veratrum and Ergot in the Treatment of Hypertension, Clarence M. Tinsley, M.D.

3:40-3:50—Recess.

3:50-4:10—Special Problems in the Management of Subacute Bacterial Endocarditis, Lowell A. Rantz, M.D.

4:10-4:30—Problems in the Management of Edema with Salt Restriction, John Luetscher, M.D.

Thursday Evening, October 26, 1950

8:00 p.m.

Colonial Ballroom, St. Francis Hotel

Presiding: WILLIAM J. KERR, M.D.

Headache—George Pickering, M.D.

Friday Morning, October 27, 1950

9:30 a.m.-12:00 m.

Presiding: DWIGHT L. WILBUR, M.D.

9:30-9:50—Lipoprotein in the Pathogenesis of Atherosclerosis, John Gofman, M.D.

9:50-10:20—Natural History and Management of Coronary Disease, A. L. Bloomfield, M.D.

10:20-10:35—Controversial Aspects of the Treatment of Myocardial Infarction: Bed Rest and Anticoagulants, David A. Rytand, M.D.

10:35-10:50—Controversial Aspects of the Treatment of Myocardial Infarction: Management of Shock and Cardiac Failure, George B. Robson, M.D.

10:50-11:00—Recess.

11:00-12:00—Coronary Circulation During Hemorrhage and Shock, Carl J. Wiggers, M.D.

Friday Afternoon, October 27, 1950

2:00 p.m.-4:40 p.m.

Presiding: CHARLES A. NOBLE, JR., M.D.

2:00-3:00—The Present Status of the Problem of Essential Hypertension, George Pickering, M.D.

3:00-3:30—Surgical Treatment of Non-Congenital Heart Disease, Emile F. Holman, M.D.

3:30-3:50—Therapy of Cardiac Arrhythmias During and After Surgical Operations, William J. Kerr, M.D.

3:50-4:00—Recess.

4:00-4:20—The Cardiac Patient as a Surgical Risk, Francis L. Chamberlain, M.D.

4:20-4:40—Sympathectomy in the Treatment of Peripheral Vascular Disease, Norman E. Freeman, M.D.

Friday Evening, October 27, 1950

Colonial Ballroom, St. Francis Hotel

7:30 p.m.

Annual Dinner Meeting

Presiding: ANN PURDY, M.D., Chairman

Adventures in Hypertension—George Pickering, M.D.

Saturday Morning, October 28, 1950

9:00 a.m.

San Francisco Hospital, Ward P

Presiding: J. MARION READ, M.D.

Presentation of Patients with Various Types of Heart Disease.

Participants: LeRoy Briggs, M.D., Maurice Eliaser, M.D., J. K. Lewis, M.D., Clayton D. Mote, M.D., Charles A. Noble, Jr., M.D., Arthur Selzer, M.D., Norman Sweet, M.D., Charles F. Sweigert, M.D., Clarence M. Tinsley, M.D., Dwight L. Wilbur, M.D.

SANTA BARBARA

The first annual session of the **Santa Barbara Medical and Surgical Institute** will be held Thursday and Friday, October 12 and 13, 1950, in Bissell Auditorium of Cottage Hospital, Santa Barbara. One of a series sponsored by the California Medical Association Committee on Postgraduate Activities, the program was arranged by the Santa Barbara County Medical Society, Postgraduate Study Committee and the Committee on Graduate and Postgraduate Medical Education of the College of Medical Evangelists.

Thursday, October 12, 1950

8:30-9:30 a.m.—Registration: Bissell Auditorium, Cottage Hospital. Registration fee of $5 entitles registrant to attend any or all of the other Postgraduate Institutes in the 1950-1951 series.

MORNING SESSION

Chairman: H. I. BURTNESS, M.D., Santa Barbara

9:30-10:30—"Clinical-Pathological Conference," directed by Carrol S. Small, M.D.

10:30-11:15—"Borderline Psychiatric Problem Cases," George T. Harding, M.D.

11:15-11:30—Intermission.

11:30-12:00—"Postgraduate Activities of the California Medical Association," John C. Ruddock, M.D.

12:00-2:00—Luncheon: Discussion groups with Institute speakers.

AFTERNOON SESSION

Chairman: V. G. MIDDLETON, M.D., San Luis Obispo

2:00-2:30—"Surgical Conditions in Infancy and Childhood," J. Norton Nichols, M.D.

2:30-3:00—"Differential Diagnosis of Jaundice," John E. Peterson, M.D.

3:00-3:15—Intermission.

3:15-4:00—"Differential Diagnosis of Intracranial Tumor and Vascular Disease," Cyril B. Courville, M.D.

4:00-4:30—"Management of Obstetrical Complications," Ralph J. Thompson, M.D.

4:30-5:00—Discussion.

7:00-9:00—Dinner: "Medicolegal Pitfalls in Medical Practice," Louis J. Regan, M.D., LL.B.

Friday, October 13, 1950

MORNING SESSION

Chairman: W. C. HUFF, M.D., Oxnard

9:00-9:30—"Use of Radioactive Iodine in Diagnosis and Treatment of Thyroid Disease," Mortimer E. Morton, M.D., Ph.D.

9:30-10:15—"Use and Abuse of Antibiotic Therapy," Albert G. Bower, M.D.

10:15-11:00—"Office Urology," Roger W. Barnes, M.D.

11:15-12:00—"Hyperventilation—Physiological and Clinical Significance," James J. Short, M.D.

12:00-2:00—Luncheon: Discussion groups with Institute speakers.

AFTERNOON SESSION

Chairman: J. W. MOORE, M.D., Ventura

2:00-2:45—"Iatrogenesis in the Field of Cardiac Diseases," William Paul Thompson, M.D.

2:45-3:15—"Value of Anorectal Examination in General Practice," Malcolm R. Hill, M.D.

3:15-3:30—Intermission.

3:30-4:15—"ACTH and Cortisone — Physiological and Therapeutic Considerations," E. Kost Shelton, M.D.

4:15—Discussion.

GENERAL

More than 75 per cent of the **medical graduates who interned in Army hospitals** under the Military Intern Training Program have remained in the Army longer than the legal requirement for active duty, according to figures released recently by Major General R. W. Bliss, the Army Surgeon-General.

Of the 311 young physicians who passed through the program, 235 elected to remain on active duty in the army medical service, either as regular or reserve officers. Of the other 76, several have requested return to active duty after a comparatively brief period of nonmilitary practice. All but seven of the 76 retained their reserve commission.

POSTGRADUATE EDUCATION NOTICES

For more complete information as to fees and time of sessions address the institutions as listed.

OCTOBER 1950

University of California at Los Angeles

Recent Advances in Obstetrics and Gynecology—One week—October 16-20.

NOVEMBER - DECEMBER 1950

University of California at Los Angeles

"Ophthalmological Aspects of the Medical Specialties." November 7 to December 12, 1950.
Note: The above class comprising six evening lectures and demonstrations will meet on Tuesday evenings, 7:30 to 9:30, at Long Beach Veteran Hospital.

DECEMBER 1950

University of California at Los Angeles

Internal Medicine—9 months full-time, December 4, 1950 to September 1951.

JANUARY 1951

University of California at Los Angeles

Advanced Hematology. January 10 to February 28. One per week.

BOOK REVIEWS

THE MERCK MANUAL OF DIAGNOSIS AND THERAPY. Eighth Edition, Merck and Co., Rahway, N. J., 1950. $4.50 Regular Edition and $5.00 Thumb-Index Edition.

According to the foreword, "this is a completely new handbook, not a revision of previous editions. More than 100 outstanding clinicians throughout the United States have served as authors or consultants and assisted the Editorial Board of 12 physicians." The book consists of two parts, the first of 1,460 pages being an expansion of the material in the previous edition and the addition of new material on diseases, major symptoms, and treatment, and part two, of 110 pages, presenting new chapters on routine immunization measures, clinical and bedside procedures, office laboratory tests, items for the doctor's bag, pre- and postoperative care, etc. Of special interest are chapters on medical emergencies, such as drowning, burns, poisoning, venomous bites, electrick shock and infusion reactions.

Each of the 20 section of Part I is ended with a comprehensive list of classified prescriptions for the treatment of symptoms and pathological physiology of the diseases discussed in the section. Each section is divided into chapters. Each chapter, in general, contains a general introductory statement about the nature of the disease; this is followed by discussions of symptoms and signs, pathology, diagnosis and treatment. There is much new material on allergies, blood cell dyscrasias, uterine bleeding, therapy of thyrotoxicosis, tetanus and malaria, indications for cortisone and ACTH, BAL, mustard gas and newer antibiotics. Surgical as well as medical diseases are discussed. The section on poisoning consists of 45 pages of briefly presented but very helpful information.

There is an up-to-date table of recommended chemotherapy in the more common infections and a table on differential diagnosis of headache.

In view of the scope of the book, with discussions of most of the medical and surgical diseases compressed to 1,570 pages, it is to be expected that many subjects are treated in a far too sketchy and unsatisfactory manner. Especially disappointing to the reviewer were sections on ulcerative colitis, pruritus ani, renal function, alcoholism and herpes, which lacked much of the newer developments.

Merck's Manual is a handy, quick reference book, useful for orientation but not for a complete discussion of any subject.

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INFANT NUTRITION—ITS PHYSIOLOGICAL BASIS. By F. W. Clements, M.D., D.P.H., D.T.M., Senior Medical Officer, Commonwealth Department of Health, Australia. The Williams and Wilkins Company, Baltimore, 1949. $4.50.

This is an excellent reference book for the obstetrician, pediatrician, and general practitioner. The subject of fetal nutrition is reviewed comprehensively. Recent studies in the field of biochemistry and physiology are summarized and applied to the clinical management of pregnancy. As might be expected in a book by an Australian, breast feeding and breast milk are discussed at great length. In that country the common lack of home refrigeration, the infrequency of pasteurization and of tuberculin testing of dairy herds, and finally the limited availability of evaporated milk all contributed to the advocacy of breast feeding during the last decade. As a result the study of the biochemistry of breast milk has been pursued more intensively in Australia than in this country. A detailed and well documented comparison of cow's milk and breast milk is made.

There follows a section on caloric and nutrient requirements of infants and children including metabolic disturbances of dietetic origin.

The contents of this book are not quite duplicated by any one American text. Perhaps a more descriptive title for it would be, "Recent advances in the study of fetal and infant nutrition with the clinical application thereof."

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MEDICINE FOR NURSES. By W. Gordon Sears, M.D. (Lond.), Senior Physician and Superintendent Mile End Hospital, London. The Williams and Wilkins Company, Baltimore, 1949. $3.00.

Since World War II most nursing schools have put greater emphasis on academic instruction than they did during the war years. Consequently textbooks are being selected not for brevity or with an eye to fulfilling minimum requirements, but for an increasingly comprehensive knowledge of basic nursing courses. Recent textbooks in medicine for nurses are larger than before, include more information about diseases, emphasize in detail the nursing aspects of diseases, and are well illustrated, some with color plates. In comparison with these newer textbooks the present volume, published in England, is inadequate. The field of medicine is too briefly covered, and many of the details of diseases with which the present graduate nurse is expected to be familiar are omitted. The medical aspects of coronary thrombosis, for example, are covered in less than one page. The term *myocardial infarction* is not mentioned and no reference is made to shock or changes of blood pressure which may occur. The pathogenesis and pathology of the condition are summed up in four sentences. Under treatment, the student nurse is told that the patient should remain in bed at least eight weeks. The use of anticoagulants is dealt with in one sentence: "Dicoumarol may be used to prevent extension of the clotting."

In most of the sections the details of nursing care are not demarcated clearly from the over-all medical treatment. This has advantages in some respects since the student is made aware of the whole therapy in a given problem—nursing as well as medical. On the other hand, a careful distinction between the duties and responsibilities of nurse and physician is not emphasized in many cases. The student might justifiably be confused as to what she is expected to do and what is the doctor's responsibility.

Terms used throughout the book are British and in some cases might cause confusion. A rubber sheet, for example, is referred to as a macintosh; phenobarbital is called phenobarbitone; chills are rigors, etc. The double-joined vowel is used throughout the text: oedema, aenemia, haemorrhage, aetiology.

There are 67 illustrations. The photographs for the most part are clear and typical of certain medical conditions. Diagrams are used to explain some of the fundamental physiologic factors involved in diseases. Although very simple, these diagrams are pertinent and basically correct in terms of classical principles. There are no colored illustrations.

This book cannot be recommended as a standard textbook in medicine for the majority of nursing schools. As a supplementary volume to be used primarily for review, or as a reference for abbreviated courses in nursing, such as those given to nurses' aides or military corpsmen, it might prove useful.

RADIOGRAPHIC ATLAS OF SKELETAL DEVELOPMENT OF THE HAND AND WRIST. Based on the Brush Foundation Study of Human Growth and Development initiated by T. Wingate Todd, M.B., Ch.B., F.R.C.S. By William Walter Greulich, M.A., Ph.D., Professor of Anatomy, Stanford University School of Medicine; S. Idell Pyle, M.S., Research Associate Brush Foundation and Department of Anatomy, Western Reserve University School of Medicine, Stanford University Press, Stanford, California, 1950. $10.00.

The publication of this atlas marks an important step toward integrating concepts of growth and development into the practice of clinical medicine. From the work of child development centers throughout the country, it has become established that the process of skeletal development is the most significant available measure of physical maturation. It is closely related to reproductive and total somatic growth and is of great clinical value, especially when considered in relation to chronological age.

With the publication by T. Wingate Todd, in 1937, of his "Atlas of Skeletal Development," clinically useful assessments of skeletal age became feasible on the basis of one standardized radiograph of the hand and wrist. Refinements of Todd's method, embodied in the present Greulich and Pyle atlas, improve the reliability of such assessments and make it possible to evaluate not only the level of development but also its uniformity. Trained observation also allows deductions about the adequacy of mineralization and about scars of interrupted growth suggesting past illness. If hand films are repeated after a suitable interval, they provide a means of determining the rate as well as the level of maturation.

The excellence of the volume lies in the clarity of its directions and in the choice of standards, many of which are taken from a successive series on the same children. There is thus very little difficulty in matching an unknown x-ray to its correct age peer.

Although the assignment of correct skeletal age to a given film requires practice and patience, still it is a method which is well within the capacity of any x-ray specialist or endocrinologist. It is to be hoped that the practice of making an accurate reading of a single hand film on the basis of these precise standards for boys and girls will replace the older, more expensive and less rewarding method of assigning skeletal age by comparing films of a large number of joints to sets of standards which are only approximate. Since the value of such readings has already become established in the study of childhood endocrine and growth problems, it is probable that the method will come into general practical use.

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PROGRESS IN CLINICAL ENDOCRINOLOGY. Edited by Samuel Soskin, M.D., Director, Medical Research Institute, Michael Reese Hospital, Chicago, Illinois; Dean, Michael Reese Hospital Post-Graduate School; Professorial Lecturer in Physiology, University of Chicago. Grune and Stratton, New York, 1950. $10.00.

The 79 papers included in this volume represent an attempt to present the subject concisely. The editor makes no claim that the work represents a complete review or textbook; some of the writings deal broadly with the subject matter, while others cover only very limited aspects. The book is written primarily for the clinician, but historical and physiological material necessary for adequate understanding is not slighted. The list of contributors is impressive; most of them are well-known authorities in their field.

In most cases, controversial matters are clearly indicated, although from the text one might assume that the evidence in favor of the "free diet" in adult diabetics is incontrovertible. Pure speculation (e.g., the possible insect transmission of endemic goiter) is, fortunately, held to a minimum.

The several papers dealing with the treatment of hyperthyroidism, utilizing antithyroid drugs, radioactive iodine, and surgery; and those concerning the diagnosis and treatment of adrenal diseases, in themselves makes the volume valuable.

The techniques and interpretation of steroid hormone assays, tools which are becoming increasingly available to the clinician, are discussed in a general manner.

The beneficial effects of testosterone in situations where protein anabolism is desired, the use of ACTH and cortisone in arthritis, and the role of hormones in the treatment of other "non-endocrine" diseases are handled adequately. Transuterine and transabdominal pneumoperitoneum in the diagnosis of pelvic disease will be of interest to the gynecologist. Gynecomastia, anorexia nervosa, cryptorchidism, infertility and antihormones are among the subjects discussed in the light of recent discovery.

In general the papers are well written. Prolixity and duplication are minimal. The book is recommended for the clinician who is not intimately acquainted with the recent literature and yet has more than a superficial interest in endocrine problems.

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YOU AND YOUR HEART—A Clinic for Laymen on the Heart and Circulation. By H. M. Marvin, M.D., T. Duckett Jones, M.D., Irvine H. Page, M.D., Irving S. Wright, M.D., and David S. Rutstein, M.D. Random House, New York, 1950. $3.00.

"You and Your Heart" is an authoritative, factual, and fascinating account of the workings and misworkings of the heart and circulatory system. It is a book designed for the layman—for anyone curious about the mechanisms of that "toughest" of all muscles, the heart, for anyone suffering from heart disease or with a family history of heart "trouble," for anyone who fears the possibility of "a stroke," "heart failure," "high blood pressure," or "hardening of the arteries"; in short, for anyone with a heart.

"You and Your Heart" was written by five of the leading experts in the cardiovascular field who collaborated to answer the questions of the average person about the heart, to explain the reasons for the prescriptions and proscriptions of the doctor, to explode some of the misconceptions about heart disease held by even the most intelligent of laymen, and to remove needless fear. A professional nonmedical writer "translated" the information into simple, vivid language that is easily understood.

This book covers a wide field. It describes the functioning of the normal heart and circulation from birth through life. It explains the most important of the diseases of the heart and blood vessels, tells how they develop and what can be done about them. It is not a book on self-treatment, but instead gives information, as Dr. Irving S. Wright puts it, "to supplement the physician's advice and, where needed, to strengthen his hand." In its factual, unexcited way, it helps to remove anxiety about heart diseases, to reassure the fearful patient and his family, and to show the person with a heart disease how he may continue to lead a productive life.

In addition—and this will be of interest to physicians as well as to the general public — "You and Your Heart" stresses the need for intelligent use, by the profession and patient alike, of the public health services, for a partnership between the physician and layman in the campaign against diseases of the heart and circulation, and, above all, for more work and more research on the cardiovascular diseases.

The book can be highly recommended.